Melanoma (unresectable, metastatic, ipilimumab naive) - pembrolizumab [ID801]

Final appraisal determination committee papers

Contents

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab

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

- How is pembrolizumab expected to be used in clinical practice? Will it be considered for people with BRAF mutations and/or people without BRAF mutations (that is, BRAF mutation-positive and/or BRAF mutation-negative)?
- The key clinical effectiveness evidence for pembrolizumab compared with ipilimumab was obtained in the KEYNOTE-006 trial.
  - This trial did not use the licensed dose of pembrolizumab. Are the results generalisable to pembrolizumab at its licensed dose?

  - The trial was stopped early, and mature overall survival data are not available. Is there sufficient evidence to infer the effect of pembrolizumab on overall survival?
  - The trial protocol specified a maximum treatment duration of 2 years for pembrolizumab, but this rule was not implemented and does not appear in the marketing authorisation. Should a maximum duration for pembrolizumab treatment be specified?
- There is very limited evidence comparing pembrolizumab with BRAF inhibitors (dabrafenib and vemurafenib) – people for whom BRAF inhibitors would be considered were excluded from KEYNOTE-006, and the only available comparisons are based on the company's network meta-analysis.
  - The ERG considered the company's network meta-analysis to be flawed. Is this analysis robust enough to inform decision making?
  - What is the Committee's view on the effectiveness of pembrolizumab compared with dabrafenib and vemurafenib?
- The company considers that dacarbazine is not an appropriate comparator in this population, but some people may consider this treatment in clinical practice. Have all the relevant comparators been included?

Cost effectiveness

- What is the Committee's view of the assumptions in the company's economic model?
  - Are the assumptions appropriate and clinically plausible?
  - Have progression-free survival and overall survival been extrapolated appropriately?
  - Has the model captured all relevant costs and benefits associated with pembrolizumab?
  - Are the company's scenario analyses informative for decision making?
  - What is the Committee's view on the robustness of the comparison with dabrafenib and vemurafenib (BRAF mutation-positive subpopulation)?
- The ERG identified limitations in the company's model and provided exploratory analyses to address these limitations.

  - Are the amendments to the company's model appropriately, and do they address the limitations?
  - What is the Committee's view of the ERG's 2 'stress-test' scenarios?
- What are the most plausible ICERs for pembrolizumab compared with ipilimumab, dabrafenib and vemurafenib, taking into account all 4 patient access schemes and the most plausible assumptions?

Other considerations

- The company proposes that pembrolizumab should be considered as an end-of-life treatment. Are the end-of-life criteria met for this appraisal?

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 pembrolizumab within its marketing authorisation for treating advanced melanoma.

1.2 The marketing authorisation for pembrolizumab covers both melanoma that has been and that has not been treated with ipilimumab. This appraisal specifically considers pembrolizumab for treating ipilimumab-untreated melanoma; a separate appraisal considers melanoma that has been previously treated with ipilimumab (ID760; first Committee discussion 29 July 2015).

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with advanced (unresectable stage III or stage IV) melanoma previously untreated with ipilimumab		–	Includes both BRAF mutation-positive and BRAF mutation-negative.
Int.	Pembrolizumab		–	Licensed dose is 2 mg/kg every 3 weeks; phase III

				trial used 10 mg/kg every 2 or 3 weeks.
Com.	• Dacarbazine • Ipilimumab • Vemurafenib (for people with BRAF V600 mutation-positive disease) • Dabrafenib (for people with BRAF V600 mutation-positive disease)	• Ipilimumab • Vemurafenib (for people with BRAF V600 mutation-positive disease) • Dabrafenib (for people with BRAF V600 mutation-positive disease)	The company considered that dacarbazine was not an appropriate comparator. It stated that dacarbazine is considered to be part of supportive care, and noted that no improvement in survival has been seen with dacarbazine, compared with supportive care, for people with advanced melanoma.	Comparison between pembrolizumab and dabrafenib or vemurafenib is based on indirect comparisons. Although dacarbazine is not included as a comparator throughout, it is included in the company's network meta-analyses; the ERG agreed with this approach.
Out.	• Progression-free survival • Overall survival • Response rate • Adverse effects of treatment • Health-related quality of life		–	Health-related quality of life data were collected in the phase III trial, but were immature at the time of submission.
Source: Final scope, company submission (table 1) and ERG report				

2 The technology and the treatment pathway

2.1 Pembrolizumab (Keytruda, Merck Sharp and Dohme) is a humanised monoclonal antibody which acts on the 'programmed death 1' protein (PD-1). This protein is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response. Pembrolizumab has a marketing authorisation in the UK as a monotherapy for treating advanced (unresectable or metastatic) melanoma in adults. Previously, pembrolizumab was available through the Early Access to Medicines Scheme from the UK Medicines and Healthcare products Regulatory Agency. Pembrolizumab is administered

intravenously over 30 minutes at a dose of 2 mg/kg every 3 weeks until disease progression or unacceptable toxicity (see Table 2).

2.2 The company that holds the marketing authorisation for pembrolizumab (Merck Sharp & Dohme) has agreed a patient access scheme with the Department of Health. This scheme provides [redacted] discount to the list price of pembrolizumab (see Table 2), applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Table 2 Technology and comparators

	Pembrolizumab	Ipilimumab	Dabrafenib	Vemurafenib	Dacarbazine
Marketing authorisation	Monotherapy, for unresectable or metastatic melanoma in adults	For unresectable or metastatic melanoma in adults	Monotherapy, for adults with unresectable or metastatic melanoma with a BRAF V600 mutation	Monotherapy, for adults with BRAF V600 mutation-positive unresectable or metastatic melanoma	As a single agent, for patients with metastasized malignant melanoma
Dosage and administration	2mg/kg every 3 weeks, until disease progression or unacceptable toxicity IV over 30mins	3mg/kg every 3 weeks for 4 doses IV over 90 mins	150mg twice daily, until the patient no longer derives benefit or has unacceptable toxicity Oral	960mg twice daily, until disease progression or unacceptable toxicity Oral	200–250mg/m^2 per day for 5 days every 3 weeks, or 850mg/m^2 every 3 weeks IV bolus or over 15–30mins
Acquisition cost [1]	50mg vial: £1315 (£[redacted] with PAS)	50mg vial: £3750	28 x 75-mg capsules: £1400	56 x 240 mg tablets: £1750	500-mg vial: £16.50
Average cost of a course of treatment [1]	£34,613 ([redacted] with PAS) [2] (mean treatment duration: 7.19 cycles)	For a 70kg person: £18,750 per course [3]	£1400 per week	£1750 per week	For a 175cm, 70kg person, 850mg/m^2 every 3 weeks: £51.55 per cycle

1: List prices taken from British national formulary online (accessed August 2015). Ipilimumab, dabrafenib and vemurafenib have confidential patient access schemes, which cannot be reported in this document. 2: Company estimates. 3: NICE technology appraisal guidance 268.

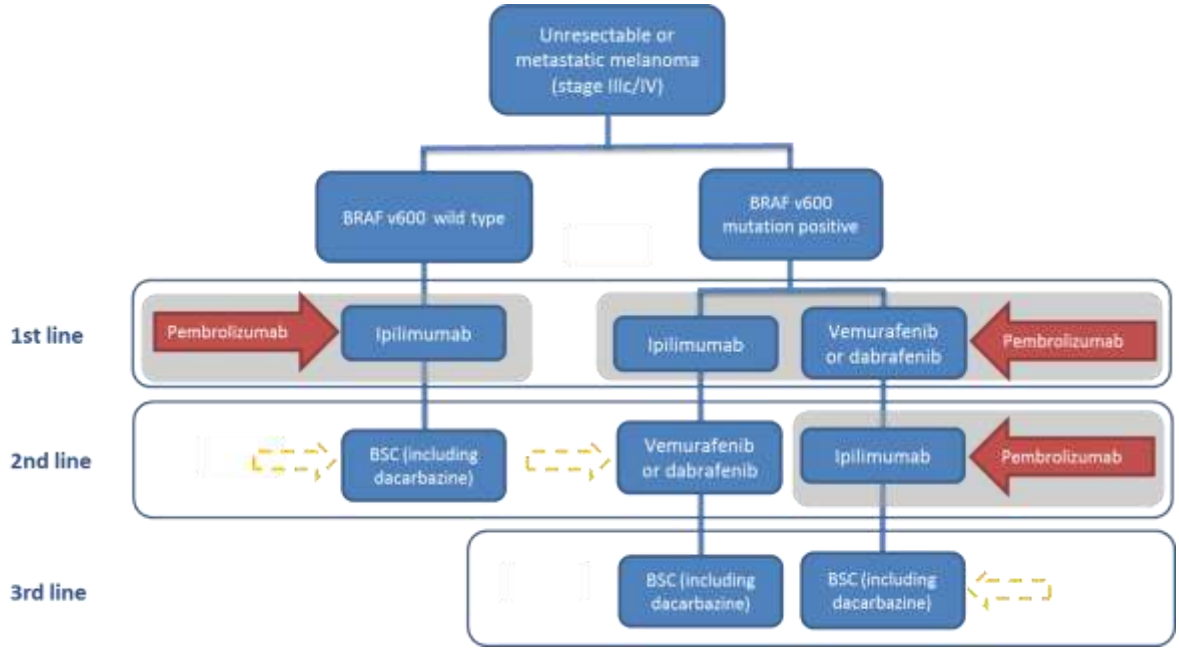
See summary of product characteristics for details on adverse reactions and contraindications.

IV, intravenous; PAS, patient access scheme.

2.3 Treatment options for metastatic melanoma include biological therapy, chemotherapy, radiotherapy and surgery. Cancers with a mutation in the 'BRAF' gene may be treated with BRAF-targeted therapy. Some people with a BRAF-mutation (particularly those with slowly progressing cancers), and those without a BRAF mutation, may be treated with ipilimumab. Technology appraisals 268 and 319 recommend ipilimumab as an option for treating advanced (unresectable or metastatic) melanoma in people who have and have not had prior therapy (respectively). NICE technology appraisal guidance 269 and 321 recommend vemurafenib and dabrafenib (respectively) as options for treating locally advanced or metastatic BRAF V600 mutation-positive unresectable or metastatic melanoma. Dacarbazine and supportive are also considered in clinical practice, when targeted or biological therapies are not suitable.

2.4 This appraisal considers pembrolizumab for people who have not previously had ipilimumab (Figure 1). The company stated that this is particularly relevant for people without a BRAF mutation, as there are few treatment options in this situation.

Figure 1 Treatment pathway



: proposed position of pembrolizumab in this appraisal. proposed position for ipilimumab-treated disease, as considered in a separate appraisal (ID760).

Developed from company submission, figure 3 (page 37) and company response to clarification for appraisal ID760.

3 Comments from consultees

3.1 Consultees emphasised that ipilimumab is valuable for people without rapidly progressing, high volume disease, noting that people must have a life expectancy of at least 3 months to benefit from this treatment. They noted that dabrafenib and vemurafenib are considered for people with a BRAF mutation and a comparatively poor prognosis (characterised by high volume disease, high lactate dehydrogenase, rapid disease progression, low performance status and brain metastases). They noted that fewer than 5% of people with BRAF mutation-negative melanoma are offered cytotoxic chemotherapy as a first-line option, to reduce tumour size before immunotherapy.

3.2 Consultees noted that there is a need for additional training and support to manage immune-related adverse events associated with pembrolizumab,

although they considered the toxicity profile of pembrolizumab to be better than ipilimumab. Consultees also highlighted the burden of delivering pembrolizumab every 3 weeks for up to 2 years, compared with the fixed course of ipilimumab. Consultees noted that there has already been considerable use of pembrolizumab through the Early Access to Medicines Scheme.

3.3 Consultees considered that the results of the KEYNOTE-006 trial (see section 4.1) provide evidence of a clinically meaningful benefit associated with pembrolizumab. However, they stated that long-term survival data is needed to ensure pembrolizumab provides durable remissions for people whose disease responds. They considered that there is not enough evidence to confirm that dose or administration frequency affects clinical outcomes.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review identified 2 clinical trials of pembrolizumab for melanoma previously untreated with ipilimumab: KEYNOTE-006 and KEYNOTE-001.

- KEYNOTE-006 was a randomised, multicentre (including centres in the UK), phase III trial comparing pembrolizumab 10 mg/kg every 2 weeks (n=279) or every 3 weeks (n=277) with ipilimumab 3 mg/kg every 3 weeks for 4 doses (n=278). Pembrolizumab therapy continued until progression, complete response or unacceptable toxicity, up to a maximum of 2 years. The study was conducted in adults with advanced or metastatic melanoma, with or without a BRAF mutation, that had been treated with up to 1 prior line of therapy and no prior ipilimumab. People with previously untreated BRAF mutation-positive tumours and a high lactate dehydrogenase level or rapidly progressing disease were excluded. The primary outcomes were progression-free survival and

overall survival, analysed in the intention-to-treat (ITT) population. Secondary outcomes included overall response rate, response duration and health-related quality of life. Results were analysed at 2 planned interim analyses, after 6 months of follow up (September 2014) and after 9–12 months of follow-up (March 2015), after which the study was stopped on the grounds of efficacy.

- KEYNOTE-001 was a combined phase I and II study, comprising an initial dose-escalation study (part A) followed by a group of phase II substudies (parts B–F). Part D was a randomised, open-label study comparing pembrolizumab 2 mg/kg every 3 weeks (n=51) with 10 mg/kg every 3 weeks (n=52), in people with advanced melanoma who had not had prior ipilimumab (up to 2 prior therapies were permitted). The primary outcome was response rate, and secondary outcomes included disease control rate, response duration, progression-free survival and overall survival. The company presented also supportive evidence from KEYNOTE-001 part B1, a non-randomised study comparing pembrolizumab 10 mg/kg every 2 weeks (n=57), 10 mg/kg every 3 weeks (n=56) and 2 mg/kg every 3 weeks (n=22). This study involved a mixture of ipilimumab-naive and ipilimumab-treated patients.

The company stated that patient characteristics were well balanced across treatment arms (Table 3). Full details of the study methods for can be found in sections 4.3–4.5 (page 47–77; KEYNOTE-006 and -001 part D) and 4.11 (page 123–128; KEYNOTE-001 part B1).

4.2 No studies that directly compared pembrolizumab with dabrafenib, vemurafenib or supportive care (including dacarbazine) in this population were identified. The company presented a network meta-analysis to compare these treatments (see section 4.9).

Table 3 Patient characteristics in KEYNOTE-006 and KEYNOTE-001 (part D)

	KEYNOTE-006			KEYNOTE-001, part D	
	Pembrolizumab 10 mg/kg Q2W n = 279	**Pembrolizumab 10 mg/kg Q3W n = 277**	**Ipilimumab 3 mg/kg Q3W n = 278**	**Pembrolizumab 2 mg/kg Q3W n = 51**	**Pembrolizumab 10 mg/kg Q3W n = 52**
Age: median (range), years	61 (18–89)	63 (22–89)	62 (18–88)	60 (35-80)	60 (26-78)
Sex: % male	57.7%	62.8%	58.3%	62.7%	59.6%
Race: % white	97.8%	97.8%	97.8%	98.0%	94.2%
ECOG status: % ECOG 0	70.3%	68.2%	67.6%	80.4%	88.5%
PD-L1 status: % positive	80.6%	79.8%	80.9%	NR	NR
BRAF status: % mutation positive	35.1%	35.0%	38.5%	39.2%	30.8%
Lines of prior therapy: % 0 1	 65.6% 34.4%	 66.8% 32.9%	 65.1% 34.9%	 45.1% 33.3%	 55.8% 28.8%
ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death 1 ligand; Q2W, every 2 weeks; Q3W, every 3 weeks Source: Company submission, table 17 (page 75) and table 18 (page 76)					

ERG comments

4.3 The Evidence Review Group (ERG) considered that the company's systematic review was adequate; although some databases were omitted, no relevant studies had been missed.

4.4 The ERG stated that KEYNOTE-006 was well designed and well conducted. It considered that the population was representative of patients seen in the UK NHS, and patient characteristics were well balanced across treatment groups. However, it noted 3 key concerns about this trial:

- The dosage of pembrolizumab used in the pivotal study (10 mg/kg every 3 weeks) does not match the licensed dose (2 mg/kg every 3 weeks). The ERG noted that the CHMP concluded in the European Public Assessment Report (EPAR) that no differences between the licensed dose and the studied dose are to be expected. The ERG

cautiously accepted the CHMP's conclusion, and considered that the dosage did not affect effectiveness. However, it cautioned that the CHMP's conclusion is largely derived from patients who have received prior ipilimumab therapy.

- The trial was stopped early because the primary endpoints had been met, so the overall survival data were immature. The ERG stated that because no formal final analysis will be conducted, it is unclear whether the true impact of pembrolizumab on survival will be identified. The ERG cited evidence that early trial closure can exaggerate the benefits of treatment.
- The trial specified a maximum treatment duration of 24 months. However, this rule was not implemented, and so the ERG considered that the effect on clinical outcomes is unknown.

Clinical trial results

KEYNOTE-006

4.5 Pembrolizumab was associated with a statistically significant increase in both progression-free survival (first interim analysis) and overall survival (second interim analysis), compared with ipilimumab (Table 4 and Figure 2). The company stated that the results were consistent when progression-free survival was assessed by independent central evaluation (using the Response Evaluation Criteria in Solid Tumours) or by the investigator (using the Immune-Related Response Criteria). Pembrolizumab was also associated with statistically significantly higher overall response rates compared with ipilimumab ($p<0.001$). There were no significant differences in progression-free survival, overall survival or overall response rates between the 2 pembrolizumab dosing regimens ($p>0.5$). Full details of the results can be found in section 4.7 of the company submission (page 78–90).

4.6 Pre-specified subgroup analyses were presented for subgroups based on age, sex, race, Eastern Cooperative Oncology Group (ECOG)

performance status, previous treatment, region and biological markers (BRAF mutation and PD-L1 expression). The treatment effect associated with pembrolizumab was generally consistent across subgroups. However, pembrolizumab every 3 weeks appeared to provide less benefit in progression-free survival when used as a second-line therapy, compared with first-line (HR 0.80 compared with 0.50; p-value for interaction 0.0427). In addition, there was no statistically significant benefit in overall survival associated with pembrolizumab in the PD-L1 negative subgroup (HR for pembrolizumab every 2 weeks and every 3 weeks compared with ipilimumab: 0.91 and 1.02 respectively), although the statistical test for subgroup interaction was not significant (p>0.1).

KEYNOTE-001

4.7 KEYNOTE-001 part D identified no statistically significant differences between pembrolizumab 2 mg/kg every 3 weeks (licensed dose) and 10 mg/kg every 3 weeks, in overall response rates (p=0.622), disease control rates (p=0.593), progression-free survival (p=0.545) or overall survival (p=0.507). The company stated that the overall response, progression-free survival and overall survival rates were similar across both arms, compared with the pembrolizumab arms of KEYNOTE-006. Full details of the efficacy analyses can be found in section 4.7 of the company submission (page 91–98); subgroup analyses are presented in appendix 6 of the company submission.

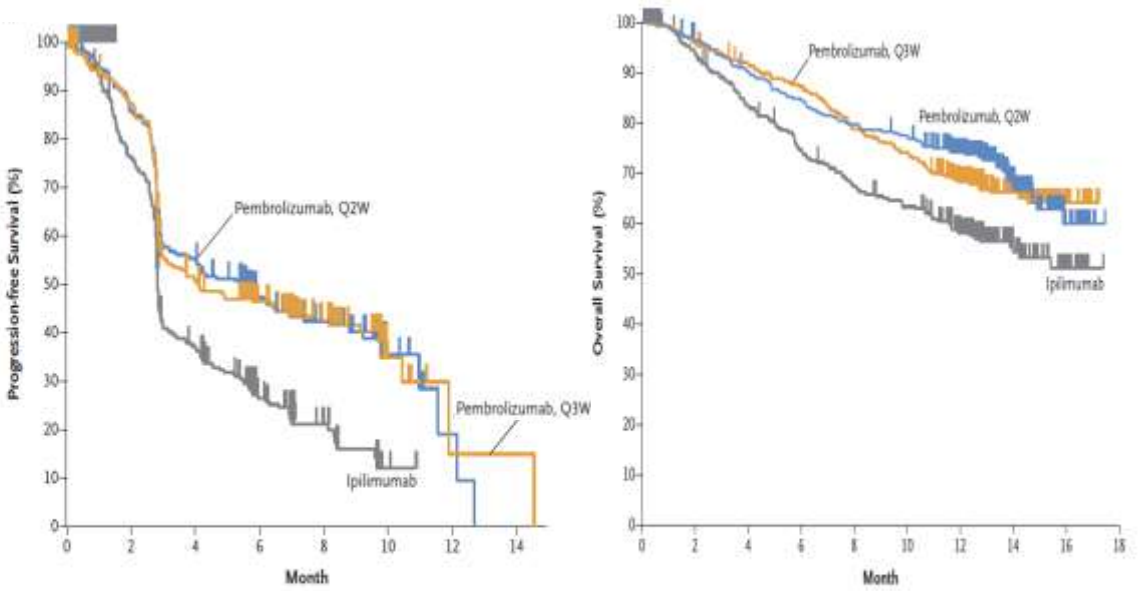
Table 4 Clinical effectiveness outcomes in KEYNOTE-006

	Pembrolizumab		**Ipilimumab** n=278
	10 mg/kg Q3W n=277	**10 mg/kg Q2W** n=279	
Progression free survival (interim analysis 1)			
Median: months (95% CI)	4.1 (2.9–6.9)	5.5 (3.4–6.9)	2.8 (2.8–2.9)
Hazard ratio versus ipilimumab (95% CI)	0.58 (0.47–0.72) p<0.00001	0.58 (0.46–0.72) p<0.00001	

Progression-free survival at 6 months: % (95% CI)	46.4 (40.3–52.3)	47.3 (41.2–53.2)	26.5 (20.9–32.4)
Overall survival (interim analysis 2)			
Median	Not reached	Not reached	Not reached
Hazard ratio versus ipilimumab (95% CI)	0.69 (0.52–0.90) p=0.00358	0.63 (0.47–0.83) p=0.00052	
Overall survival at 6 months: % (95% CI)	87.3 (82.7–90.7)	84.8 (80.0–88.5)	74.5 (68.7–79.4)
Overall response (interim analysis 1)			
Overall response rate: n, % (95% CI)	91, 32.9% (27.4–38.7)	94, 33.7% (28.2–39.6)	33, 11.9% (8.3–16.3)
Difference versus ipilimumab: % (95% CI)	17.2 (9.5, 25.6) p=0.00002	16.1 (7.8, 24.5) p=0.00013	
CI, confidence interval; Q2W, every 2 weeks; Q3W, every 3 weeks Source: company submission, table 21 (page 79)			

Figure 2 Progression-free survival and overall survival in KEYNOTE-006

A, Progression-free survival at the first interim analysis; **B**, overall survival at the second interim analysis



Source: Company submission, figures 8 (page 81) and 11 (page 87)

4.8 Health-related quality of life was measured in KEYNOTE-006, using the European Organisation for Research and Treatment Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the EuroQol EQ-5D. However,

the results were not presented in the clinical effectiveness section of the company submission, although the EQ-5D data were used in the company's economic model (see section 5.6). The results showed that there was no statistically significant difference between pembrolizumab and ipilimumab.

Network meta-analyses

4.9 The company presented a series of network meta-analyses to compare pembrolizumab with ipilimumab, dabrafenib, vemurafenib and dacarbazine. The analysis was performed in a Bayesian framework using a fixed-effects model. It was based on data from KEYNOTE-006 and 5 other trials identified in the systematic review. Results were presented for 4 scenarios: 2 of previously untreated cancers (first-line setting), and 2 also including previously treated disease (second-line setting). The company considered scenarios 2 (first-line) and 3b (both lines) to be the most trustworthy: these scenarios excluded the trial by Hersh et al. (2011), which did not present progression-free survival data and included treatment crossover that could not be adjusted for. Because of limitations in the data, no analysis was performed for dabrafenib and vemurafenib as second-line treatments. The analysis assumed that pembrolizumab 2 mg/kg every 3 weeks was equivalent in efficacy to 10 mg/kg every 3 weeks, and that BRAF mutation status does not modify the treatment effect for pembrolizumab, ipilimumab or dacarbazine. Full details of the network meta-analysis methods and assumptions can be found in section 4.10 (page 105–113) and appendices 7–11 of the company submission.

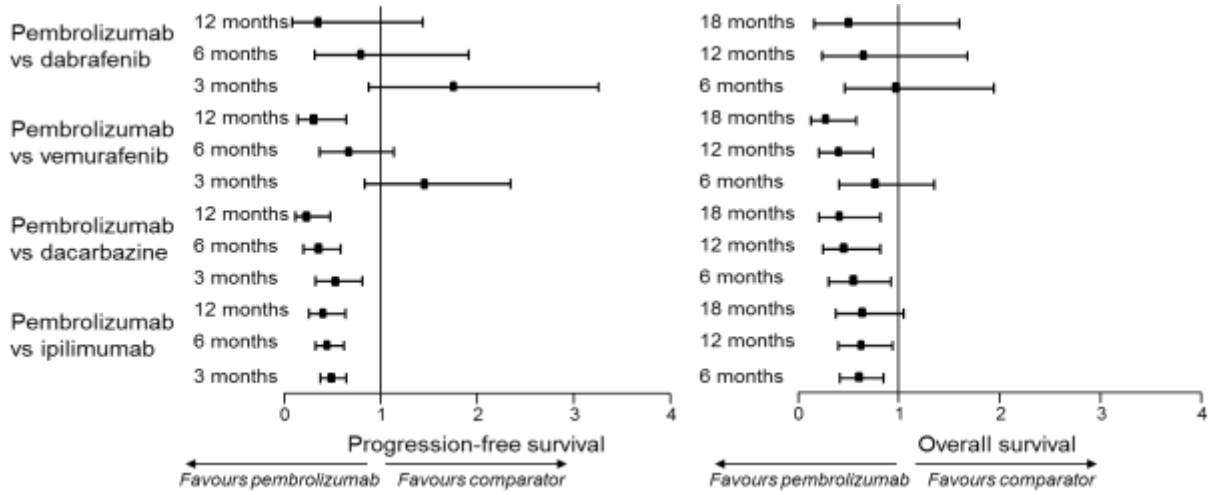
4.10 The company stated that the network meta-analysis showed that in the first-line setting, pembrolizumab appeared to have a similar efficacy to vemurafenib and dabrafenib. It noted that when the treatment effects were extrapolated, pembrolizumab appeared to be beneficial after 1 year of follow-up. The company highlighted that pembrolizumab was associated with greater progression-free survival and overall survival than both ipilimumab and dacarbazine in the first-line setting, and was at least as

efficacious as ipilimumab in the second-line setting. The results of scenario 3b are summarised in Figure 3; full results can be found in section 4.10 (page 114–119) and appendix 12 of the company submission.

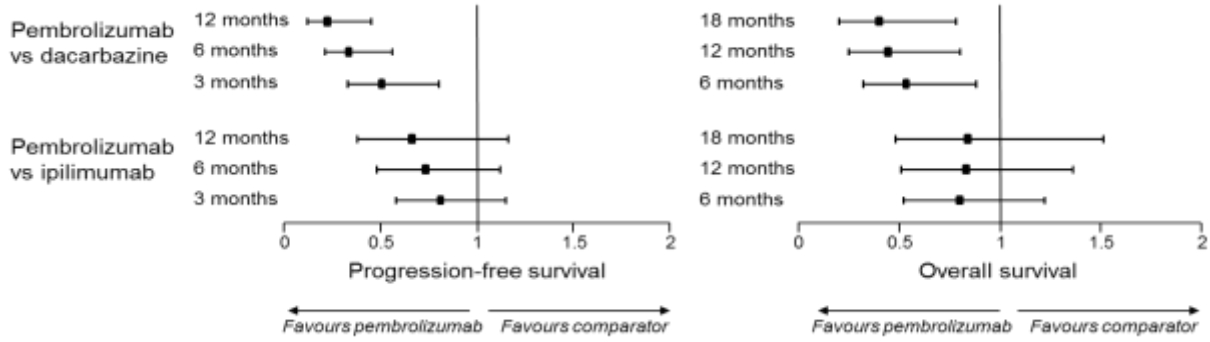
Figure 3 Results of the company's network meta-analysis (scenario 3b)

Results are presented as hazard ratios with 95% credible intervals, for pembrolizumab compared with each comparator.

First line at different time points



Second line at different time points



Source: developed from company submission, tables 42–49 (page 114–119).

ERG comments

4.11 The ERG agreed with the company that scenarios 2 and 3b were the most reliable in the company's network meta-analysis. The ERG considered that the clinical assumptions used in the network meta-analysis were

reasonable, and noted that most of the trials had a low risk of bias. However, it outlined 3 key concerns about the analyses:

- The patient populations in the control arms used to compare pembrolizumab with dabrafenib and vemurafenib are not comparable. The ERG noted important differences in age, sex and health characteristics (table 31, page 65, of the ERG report), and considered that reliable comparisons between these drugs was not possible.
- The methods did not correctly reflect changing hazard ratios over time in clinical trials. The ERG noted that the company selected methods to reflect the fact that the assumption of proportional hazards was not met. However, comparing the network meta-analysis results with the KEYNOTE-006 trial data showed that the analysis did not reliably estimate long-term effectiveness.
- The methods used to adjust for treatment switching (crossover) in the BRIM-3 trial may not have adequately adjusted for this effect. The ERG considered that the treatment effect for pembrolizumab compared with vemurafenib may have been overestimated.

The ERG concluded that the methods of the network meta-analysis were flawed. It considered that these analyses do not provide valid treatment effect estimates, particularly for pembrolizumab compared with dabrafenib and vemurafenib.

Adverse effects of treatment

4.12 The company presented detailed adverse event data from KEYNOTE-006 in section 4.12.2 (page 132–141) of its submission. These results are summarised in Table 5. The company stated that pembrolizumab was generally well tolerated. The most common treatment-related adverse events with both pembrolizumab and ipilimumab were fatigue, diarrhoea, rash and pruritus. There was 1 drug-related death with ipilimumab and none in either pembrolizumab arm. The company reported that most

categories of adverse events were similar between the 2 pembrolizumab regimens.

Table 5 Summary of adverse events in KEYNOTE-006

	Ipilimumab		Pembrolizumab (both arms combined)	
	n	%	n	%
N	256		555	
Patients with 1 or more AE	239	93%	539	97%
Toxicity grade 3–5 AE	94	37%	197	35%
SAE	77	30%	140	25%
Discontinued due to an AE	34	13%	50	9%
Drug-related AEs				
Patients with 1 or more AE	187	73%	423	76%
Fatigue	39	15%	111	20%
Diarrhoea	58	23%	87	16%
Rash	37	14%	78	14%
Pruritus	65	25%	79	14%
Immune-related AEs				
Patients with 1 or more AE	47	18%	109	20%
Toxicity grade 3–5 AE	30	12%	30	5%
SAE	27	11%	28	5%
Discontinued due to an AE	14	5%	15	3%

AE, adverse event; SAE, serious adverse event

Source: company submission, tables 56–60 (page 134–140)

ERG comments

4.13 The ERG agreed with the company that pembrolizumab appeared to be well tolerated. However, it noted the high frequency of drug-related

adverse events in both the ipilimumab and pembrolizumab arms of KEYNOTE-006.

4.14 The ERG noted that adverse event data extracted from all the trials included in the company's network meta-analysis showed that dabrafenib and dacarbazine seemed to be associated with fewer adverse events than the other treatments. It noted high rates of discontinuation due to adverse events and grade 3–5 immune-related adverse events associated with ipilimumab in combination with dacarbazine (Robert et al. [2011]), and high rates of skin-related adverse events associated with ipilimumab in all trials except KEYNOTE-006. The ERG stated that it was difficult to draw conclusions about the safety and tolerability of the drugs using these data.

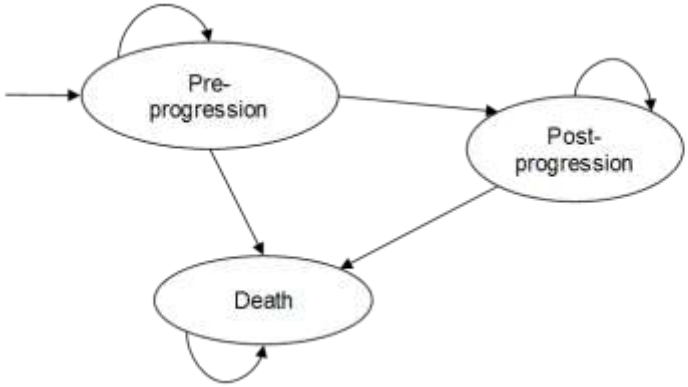
5 Cost-effectiveness evidence

5.1 The company presented an economic model comparing pembrolizumab (at its licensed dose of 2 mg/kg every 3 weeks) with ipilimumab, dabrafenib and vemurafenib, for treating advanced or metastatic melanoma that had not been previously treated with ipilimumab. It presented the analysis for 2 sub-populations: people with a BRAF mutation (in which pembrolizumab was compared with all comparators) and those without a BRAF mutation (comparing with ipilimumab only).

Model structure

5.2 The company presented a partitioned survival model with 3 states: pre-progression, post-progression and death (Figure 4). Patients received treatment with pembrolizumab, dabrafenib or vemurafenib until disease progression, or ipilimumab for 4 cycles; after progression (that is, in the 'post-progression' state), they switched to supportive care. The model used a cycle length of 1 week and had a time horizon of 30 years (lifetime). The model perspective was the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 3.5% per year.

Figure 4 Company's model structure



ERG comments

5.3 The ERG's critique suggested that the company's model was generally consistent with the NICE reference case, although it did not include cost for Personal Social Services or any impact on carers.

5.4 The ERG expressed concern that the structure of the model led to counterintuitive results – specifically, that pembrolizumab became more cost effective when its effectiveness at preventing disease progression was reduced.

Model details

5.5 The proportion of people in the each health state in each cycle was based on estimates of progression-free survival and overall survival, using a partitioned-survival (or 'area under the curve') approach. For each drug, progression-free survival and overall survival curves were developed by combining short-term clinical trial data with longer-term extrapolations. Progression-free survival was estimated as follows:

- For pembrolizumab and ipilimumab, Kaplan–Meier curves from KEYNOTE-006 (for progression-free survival based on central assessment using the Response Evaluation Criteria in Solid Tumours [RECIST] criteria) were used for the first 13 weeks, after which a parametric curve was used to extrapolate long-term outcomes. Based

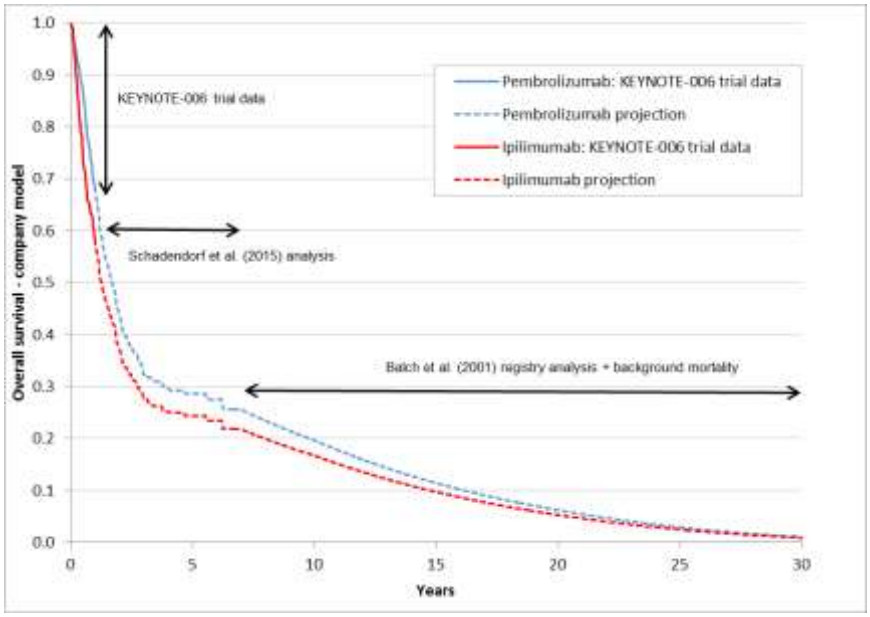
on the assumption of proportional hazards, the company identified a Gompertz model as the best fit to the observed data.

- For dabrafenib and vemurafenib, Kaplan–Meier curves from each drug's pivotal trial (BREAK-3 and BRIM-3 respectively) were used for the first 39 weeks. After this, a monthly risk of progression was applied, taken from technology appraisal 319 (ipilimumab for previously untreated melanoma).

Overall survival was estimated as follows (Figure 5):

- For pembrolizumab and ipilimumab, Kaplan–Meier data from KEYNOTE-006 were used for the first year. After this point, survival was extrapolated. The company stated that standard parametric curves gave implausible predictions. The company therefore applied conditional survival estimates taken a previously untreated cohort in a published study of long-term survival with ipilimumab (Schadendorf et al. [2015]), for 7 years. For the remainder of the model, survival was based on melanoma-specific mortality rates in a published registry study (Balch et al [2001]), combined with a background mortality rate.
- For dabrafenib and vemurafenib, Kaplan–Meier curves from each drug's pivotal trial (BREAK-3 and BRIM-3 respectively) were used for the first 60 weeks, adjusted to match patient characteristics in KEYNOTE-006. After this, survival was extrapolated consistently with technology appraisal 319, applying monthly risks of death up to week 200, followed by melanoma-specific mortality rates from Balch et al (2001) combined with a background mortality rate.

Figure 5 Overview of the company's modelling of overall survival



Source: ERG report, figure 8 (page 96)

5.6 The company modelled utility scores by assuming that quality of life decreases as people approach the last months of life (referred to as a 'time to death' approach). The company defined 6 categories based on the amount of time before the person dies, and applied a utility score to each. As deaths occurred in the model, utility scores from each category were added to the corresponding preceding model cycles. The utility scores for each category were calculated using quality of life data from KEYNOTE-006, measured using the EuroQol EQ-5D questionnaire; the scores decreased from 0.82 (more than 360 days before death) to 0.33 in the 30 days before death. The company assumed that the effect of adverse events on quality of life were captured within the KEYNOTE-006 data, so did not include any additional effects. Utility scores were adjusted for age by applying a utility decrement as age increases between 60 and 75 years (0.0039 per year).

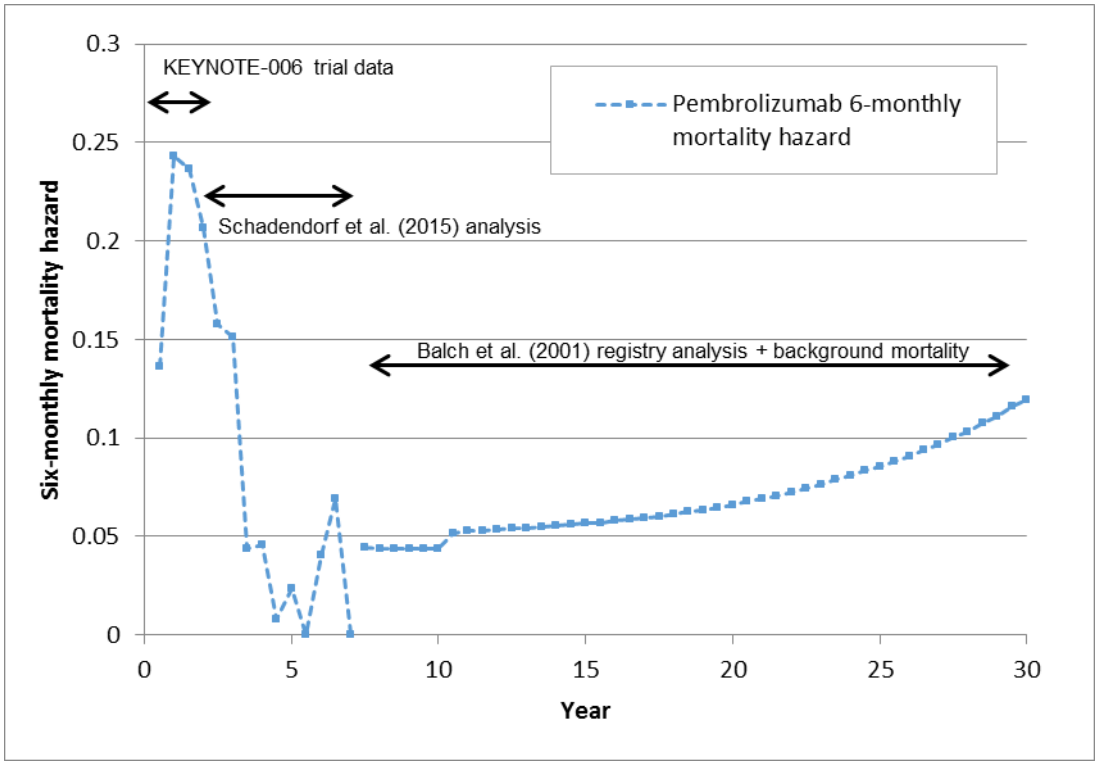
5.7 The model included costs associated with melanoma treatment, costs in each health state, management of adverse events and complications, and care at the end of life. Treatment costs included drug acquisition (where appropriate, based on patients' weight in the European cohort of

KEYNOTE-006 and assuming no vial sharing), administration, dispensing and any accompanying tests. All 4 drugs in the model have confidential patient access schemes (PASs); results based on all 4 PASs were presented by the ERG in a confidential appendix to its report and cannot be reported here. Health state costs were based on a study of resource use for melanoma treatment in the UK (MELODY; Lorigan et al. [2014]). Adverse event costs were based on the incidences in the KEYNOTE-006, BRIM-3 and BREAK-3 trials and costs for each event taken from technology appraisal 319.

ERG comments

5.8 The ERG expressed concerns about the modelling of survival. It noted that overall survival was modelled using 3-phase approaches for each drug (section 5.5). For pembrolizumab and ipilimumab, the ERG considered that although the first phase (year 1) was modelled appropriately, the second phase (years 2 to 7) was limited by a large risk of selection bias in the study by Schadendorf et al. (2015). It also considered that there were limitations in the third phase of the extrapolation (year 7 to 30), resulting from the omission of more recent registry data and the incorrect assumption that all people in the model were previously untreated at the start of the model. The ERG stated that the modelling of mortality risk over time for pembrolizumab was erratic (Figure 6) and was not clinically plausible. For dabrafenib and vemurafenib, the ERG considered that survival estimates in the first phase were unreliable, because of limitations in the algorithm used to adjust the patient characteristics. Although the ERG was satisfied with the approach for the second phase, it considered that more recent registry data should have been used for the third phase.

Figure 6 Mortality risk over time in the company model



Source: ERG report, figure 9 (page 98)

5.9 The ERG noted 4 key concerns about the modelling of progression-free survival:

- The model used evidence based on central assessment of progression. The ERG considered that investigator-assessed progression would be more representative of clinical practice.
- The ERG considered that it would have been more appropriate to use an alternative non-informative censoring rule to avoid biasing estimates of progression-free survival.
- Extrapolation of progression-free survival was based on an assumption of proportional hazards, but the ERG considered that this assumption was not appropriate. It stated that the difference in progression-free survival associated with pembrolizumab was not valid.
- Progression-free survival data for dabrafenib and vemurafenib were based on evidence from the BREAK-3 and BRIM-3 trials, but the data

were not adjusted for differences in patient characteristics between those trials and KEYNOTE-006 (that is, the population in the model).

5.10 The ERG also considered that there were limitations in the company's modelling of treatment duration, and direct treatment costs. It noted that the company modelled treatment duration using progression-free survival, but reported that this may over-estimate treatment duration as it does not take into account discontinuation due to adverse events. The ERG proposed that time to discontinuation data may be more accurate, although such data were not available for vemurafenib or dabrafenib. The ERG stated that the modelling of direct treatment costs could be improved by using a weight distribution that was more representative of the UK population (rather than from KEYNOTE-006), and by assuming the same administration cost for pembrolizumab and ipilimumab.

5.11 The ERG considered that there were 2 limitations in the utility values. Firstly, the company used EQ-5D data from all patients in KEYNOTE-006, regardless of region, and the ERG considered that UK or European patients may provide more relevant EQ-5D scores. Secondly, the company assumed that there was no change in utility on disease progression, which contributed to the counterintuitive finding that pembrolizumab appears more cost effective the less effective it becomes in preventing progression; the ERG considered that including a decrease in utility after progression may mitigate this flaw in the model.

Company's base-case results and sensitivity analysis

5.12 The company presented base-case results using the PAS price for pembrolizumab and the list prices for all other drugs; results based on all 4 PASs were presented by the ERG in a confidential appendix to its report and cannot be reported here. Full details of the base case results, including clinical outcomes and disaggregated costs, can be found in section 5.7 (page 211–218) 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 218–226).

5.13 In the base case, pembrolizumab provided a total of 3.14 quality-adjusted life years [QALYs], at a cost of £76,689. In the BRAF mutation-positive sub-population, pembrolizumab dominated (that is, provided more QALYs at lower cost than) both vemurafenib and ipilimumab. It was more costly and more effective than dabrafenib, with an incremental cost-effectiveness ratio (ICER) of £5,852 per QALY gained (Table 6). Similarly, in the BRAF mutation-negative sub-population, pembrolizumab dominated ipilimumab, providing 0.44 additional QALYs with a saving of £21,185 (Table 6).

Table 6 Results of the company's base-case analysis (including pembrolizumab patient access scheme, list price for all comparators)

A, BRAF mutation-positive sub-population

	Total cost	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALYs	ICER (£/QALY)
Dabrafenib	£71,029	3.41	2.17	-	-	-	-
Pembrolizumab	£76,689	5.08	3.14	£5,660	1.67	0.97	£5,852
Vemurafenib	£83,384	2.74	1.73	£6,695	-2.34	-1.40	Dominated
Ipilimumab	£97,873	4.37	2.69	£21,185	-0.71	-0.44	Dominated

B, BRAF mutation-negative sub-population

	Total cost	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALYs	ICER (£/QALY)
Pembrolizumab	£76,689	5.08	3.14	-	-	-	-
Ipilimumab	£97,873	4.37	2.69	£21,185	-0.71	-0.44	Dominated

ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years

Dominated: provides fewer QALYs at greater cost than the comparator

Source: company submission, tables 86 and 87 (page 211)

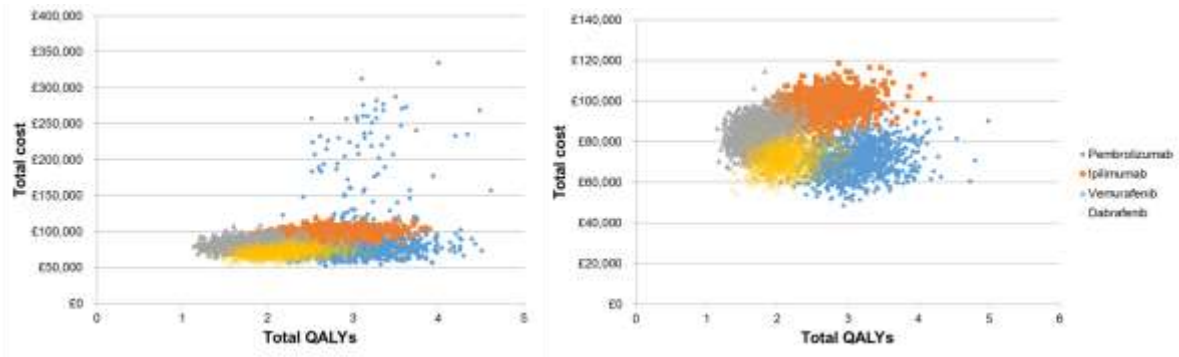
5.14 In a deterministic sensitivity analysis, the model results for all comparisons were most sensitive to the extrapolation of progression-free

survival for pembrolizumab (shape and treatment effect in the Gompertz model).

5.15 In a probabilistic sensitivity analysis (Figure 7), the total costs associated with pembrolizumab increased by £10,996 compared with the deterministic results, and the total QALYs decreased by 0.02. The results for ipilimumab, dabrafenib and vemurafenib did not change substantially compared with the deterministic analysis (change in costs £200–£600, change in QALYs 0.01–0.02). The company stated that the change in the results for pembrolizumab was due to uncertainty in the extrapolation of progression-free survival from KEYNOTE-006, leading to a small number of iterations with high treatment costs. It noted that when the duration of pembrolizumab treatment was limited to a maximum of 2 years, the probabilistic sensitivity analysis gave similar results to the deterministic analysis (Figure 7).

Figure 7 Scatterplots of the company's probabilistic sensitivity analyses for the BRAF mutation-positive sub-population

A, no maximum treatment duration; **B**, maximum 2 years pembrolizumab treatment



QALY, quality-adjusted life year

Source: company submission, figures 43 and 47 (page 222 and 226)

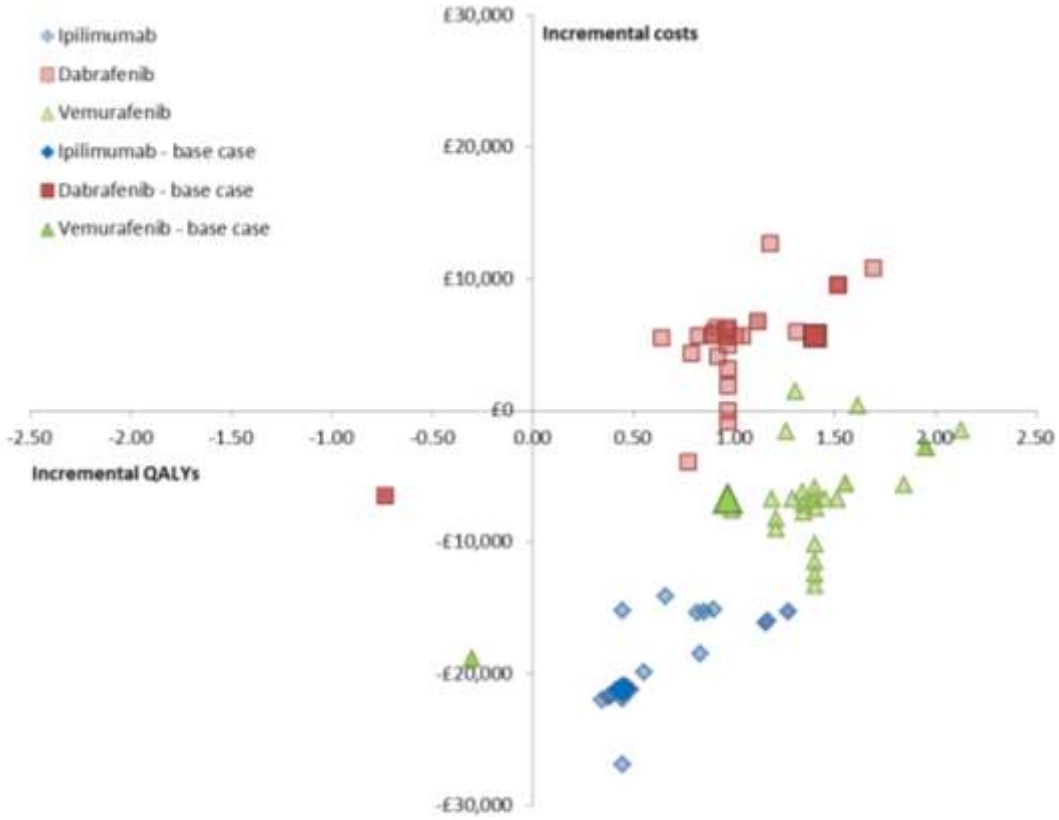
Company scenarios

5.16 The company presented 33 scenarios exploring a number of assumptions, including:

- Extrapolation methods, hazard ratios and baseline-adjustment for progression-free survival and overall survival (21 scenarios)
- Time horizon (3 scenarios)
- Utility estimates (4 scenarios)
- Treatment and terminal care costs (3 scenarios)
- Limiting treatment duration for pembrolizumab
- Omission of discounting.

5.17 The results of the scenarios are summarised in Figure 8. In most scenarios, there was an increase in incremental QALYs with pembrolizumab compared with ipilimumab and vemurafenib, and a decrease compared with dabrafenib. Incremental costs associated with pembrolizumab changed by up to £12,000 compared with the base case. The company commented that the scenarios with the biggest effect on the result were those in which overall survival was modelled using a log-normal curve, and considered that these scenarios were not clinically plausible. The company stated that these analyses showed that the cost effectiveness of pembrolizumab is robust to most sources of uncertainty.

Figure 8 Results of the company scenario analyses (including pembrolizumab patient access scheme, list price for all comparators): incremental costs and QALYs for pembrolizumab compared with ipilimumab, dabrafenib and vemurafenib



QALY, quality-adjusted life year

Source: developed from company model

ERG comments

5.18 The ERG highlighted that the 75–90% of the cost differences between treatments in the company's model could be attributed to direct treatment costs (that is, drug acquisition and administration). In addition, 87.5% of the health gain with pembrolizumab, in terms of survival, occurred after 12 months. These observations suggest that the key factors affecting health and cost outcomes in the model are drug costs, duration of treatment and overall survival gain (and in particular the extrapolation approach).

ERG exploratory analyses

5.19 The ERG made several changes to the company's model to explore the impact of addressing their principal concerns:

- ERG's preferred overall survival extrapolation and non-cancer mortality amendment (R1)
  - Because the ERG found the company's estimates of overall survival implausible, it applied an alternative approach that it had developed during an earlier appraisal (technology appraisal 268 [ipilimumab for previously treated melanoma]). This approach applied constant hazard rates based on the updated registry data (Balch et al [2009]) to 2 sub-populations (people with high mortality rates and a smaller group with excellent survival prospects), leading to a mixed exponential distribution that was used to generate expected overall survival profiles for each drug.
  - The ERG also adjusted the non-cancer mortality rates to allow for differences between males and females.
- ERG's preferred progression-free survival estimates (R2)
  - The ERG's preferred approach used investigator-assessed progression data from KEYNOTE-006. It was not possible to revise the progression-free survival estimates for the two BRAF inhibitors (vemurafenib and dabrafenib).
- Treatment duration based on time to discontinuation rather than progression-free survival (R3)
  - The ERG modified the company's model using time-to-discontinuation data directly from KEYNOTE-006 during the first year, followed by extrapolation using an exponential distribution (pembrolizumab only; ipilimumab retained the 4-cycle limit in the marketing authorisation). No time-to-discontinuation data were available from the trials of the BRAF inhibitors so these treatments were assumed to continue until progression or unacceptable toxicity.
- Utilities based on disease progression as well as time to death (R4)

  - The ERG applied utility scores to each category in the 'time to death' approach (see section 5.6), using EQ-5D data from European patients in KEYNOTE-006 only.
  - The ERG also applied a change in utility between the pre-progression and post-progression states, based on corresponding data from KEYNOTE-006.
- Drug dosages based on a UK population (R5)
  - The ERG calculated drug dosages using a body-weight profile from the Health Survey for England.
- ERG's preferred drug administration costs (R6)
  - The ERG applied the same drug administration costs to ipilimumab and to pembrolizumab.

The effects of these changes are summarised in Table 7.

5.20 The ERG also conducted 2 scenario analyses to 'stress-test' the model, by exploring the impact of extending treatment with pembrolizumab. In the first scenario, the ERG assumed that any patient in the pre-progression state after 2 years remained in this state for a further 3 years before returning to a constant risk of progression. The second scenario followed the same pattern as the first, but extended the pre-progression state by a further 3 years (that is, a total of 6 years before returning to a constant risk of progression). The results of these scenarios are presented in Table 7.

5.21 The ERG presented results of the economic model, incorporating the patient access schemes for all 3 comparators (in addition to that for pembrolizumab). These results are presented in a confidential appendix available to the Committee, and cannot be reported here.

Table 7 ERG exploratory analyses

A, Pembrolizumab versus ipilimumab (BRAF mutation-positive and BRAF mutation-negative sub-populations)

ERG model amendment	Pembrolizumab		Ipilimumab				
	Cost	QALYs	Cost		QALYs		ICER
			Total	Incr	Total	Incr	
Company's base case	**£76,689**	**3.14**	**£97,873**	**-£21,185**	**2.69**	**0.44**	**Pembrolizumab dominates**
ERG's preferred overall survival extrapolation and non-cancer mortality amendment (R1)	£80,029	3.61	£100,887	-£20,858	3.12	0.49	Pembrolizumab dominates
ERG's preferred progression-free survival estimates (R2)	£79,131	3.14	£97,883	-£18,752	2.69	0.44	Pembrolizumab dominates
Treatment duration based on time to discontinuation rather than progression-free survival (R3)	£81,123	3.14	£93,826	-£12,703	2.69	0.44	Pembrolizumab dominates
Utilities based on disease progression as well as time to death (R4)	£76,689	2.57	£97,873	-£21,185	2.17	0.40	Pembrolizumab dominates
Drug dosages based on a UK population (R5)	£75,519	3.14	£96,494	-£20,975	2.69	0.44	Pembrolizumab dominates
ERG's preferred drug administration costs (R6)	£76,689	3.14	£97,636	-£20,947	2.69	0.44	Pembrolizumab dominates
Base case + (R1:R6)	**£83,282**	**2.96**	**£95,315**	**-£12,034**	**2.52**	**0.44**	**Pembrolizumab dominates**
Base case + (R1:R6) + Scenario 1	**£92,519**	**2.98**	**£95,315**	**-£2,796**	**2.52**	**0.46**	**Pembrolizumab dominates**
Base case + (R1:R6) + Scenario 2	**£100,853**	**3.00**	**£95,315**	**£5,538**	**2.52**	**0.47**	**£11,678**

B, Pembrolizumab versus vemurafenib and dabrafenib (BRAF mutation-positive sub-population)

ERG model amendment	Pembrolizumab		Vemurafenib					Dabrafenib				
	Cost	QALYs	Cost		QALYs		ICER	Cost		QALYs		ICER
			Total	Incr	Total	Incr		Total	Incr	Total	Incr	
Company's base case	**£76,689**	**3.14**	**£83,384**	**-£6,695**	**1.73**	**1.40**	**Pembrolizumab dominates**	**£71,029**	**£5,660**	**2.17**	**0.97**	**£5,852**
R1	£80,029	3.61	£90,411	-£10,382	2.72	0.88	Pembrolizumab dominates	£74,267	£5,762	2.63	0.98	£5,868
R2	£79,131	3.14	£83,384	-£4,252	1.73	1.40	Pembrolizumab dominates	£71,029	£8,103	2.17	0.97	£8,377
R3	£81,123	3.14	£83,384	-£2,140	1.73	1.40	Pembrolizumab dominates	£71,029	£10,095	2.17	0.97	£10,437
R4	£76,689	2.57	£83,384	-£6,695	1.42	1.15	Pembrolizumab dominates	£71,029	£5,660	1.77	0.80	£7,090
R5	£75,519	3.14	£83,384	-£7,865	1.73	1.40	Pembrolizumab dominates	£71,029	£4,490	2.17	0.97	£4,628
R6	£76,689	3.14	-	-	-	-	-	-	-	-	-	-
Base case + (R1:R6)	**£83,282**	**2.96**	**£90,411**	**-£7,130**	**2.23**	**0.73**	**Pembrolizumab dominates**	**£74,267**	**£9,014**	**2.15**	**0.81**	**£11,077**
Base case + (R1:R6) + Scenario 1	**£92,519**	**2.98**	**£90,411**	**£2,108**	**2.23**	**0.75**	**£2,796**	**£74,267**	**£18,252**	**2.15**	**0.83**	**£21,903**
Base case + (R1:R6) + Scenario 2	**£100,853**	**3.00**	**£90,411**	**£10,442**	**2.23**	**0.77**	**£13,532**	**£74,267**	**£26,586**	**2.15**	**0.85**	**£31,242**

ICER, incremental cost-effectiveness ratio; incr, incremental; QALY, quality-adjusted life year

Source: ERG report, tables 55–57

Innovation

5.22 The company stated that pembrolizumab should be considered innovative in its potential to make a significant and substantial impact on health-related benefits. It noted:

- Pembrolizumab was granted a Breakthrough Therapy Designation by the US Food and Drug Administration (FDA), and was the first product to be approved under the MHRA's Early Access to Medicines Scheme (EAMS), for treating melanoma that had been previously treated with ipilimumab.
- Pembrolizumab has a novel and innovative model of action, and meets an important unmet medical need by offering an additional treatment option for a life-threatening and debilitating condition.
- Pembrolizumab significantly improves progression-free survival and overall survival, compared with current first-line therapies for advanced melanoma, and is expected to provide a durable response for a significant proportion of people. It is well tolerated, with fewer high-grade toxic events than other available drugs and manageable immune-related adverse events.

6 End-of-life considerations

6.1 The company proposed that pembrolizumab should be considered as an end-of-life treatment Table 8.

Table 8 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median overall survival, for people with previously untreated melanoma: • Treated with ipilimumab: 13.5 months • Treated with vemurafenib: 13.6 months (BRAF positive) • Treated with dabrafenib: 20.1 months (BRAF positive)

<table>
<tr>
<td>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</td>
<td>Economic model results:
<table>
<tr><th></th><th rowspan="2">Life years gained</th><th colspan="2">Life extension with pembrolizumab</th></tr>
<tr><th>Years</th><th>Months</th></tr>
<tr><td>Pembrolizumab</td><td>5.08</td><td></td><td></td></tr>
<tr><td>Ipilimumab</td><td>4.37</td><td>0.71</td><td>8.52</td></tr>
<tr><td>Dabrafenib</td><td>3.41</td><td>1.67</td><td>20.04</td></tr>
<tr><td>Vemurafenib</td><td>2.74</td><td>2.34</td><td>28.08</td></tr>
</table></td>
</tr>
<tr>
<td>The treatment is licensed or otherwise indicated for small patient populations</td>
<td>Estimated number of people for whom pembrolizumab may be considered in 2016: 1304
(Estimated 11,366 people diagnosed with melanoma in 2012, of whom 10% have stage IIIc or IV disease; 3.5% increase in incidence per year)</td>
</tr>
</table>

Source: company submission, tables 64 (page 152), 86 and 87 (page 211), and 103 (page 242)

ERG comments

6.2 The ERG agreed that people with metastatic melanoma have a life-expectancy less than 24 months, and that pembrolizumab is licensed for a small population. It considered that pembrolizumab offers a mean overall survival gain of 4 months compared with ipilimumab. However, it stated that it was uncertain whether pembrolizumab offers a mean life extension greater than 3 months compared with dabrafenib and vemurafenib, because of methodological weaknesses in the comparison of progression-free survival and overall survival between these 3 drugs.

7 Equality issues

7.1 No equality issues were raised during the scoping process. The company stated that it did not believe there were any issues relating to equality for this appraisal.

8 Authors

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

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003820/WC500190992.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for treating advanced melanoma in people previously untreated with ipilimumab [ID801]

Merck Sharp & Dohme: Evidence submission

29th May 2015

File name	Version	Contains confidential information	Date
		Yes	

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Abbreviations

Abbreviation	Definition
AACR	American Association of Cancer Research
AE	Adverse Event
AEOSI	Adverse events of special interest
AIC	Akaike Information Criterion
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BIC	Bayesian Information Criterion
BOR	Best Overall Response
BRAF	Protein kinase of the mitogen-activated protein kinase (MAPK) pathway
BSC	Best Supportive Care
CDF	Cancer Drugs Fund
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CR	Complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DCR	Disease control rate
DMC	Data Monitoring committee
DSMC	Data and safety monitoring committee
DSU	Decision Support Unit
DTIC	Dacarbazine
EAMS	Early Access to Medicines Scheme
EAP	Expanded Access Programme
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC-QLQC30	European Organisation for Research and Treatment Cancer Quality of Life Questionnaire
EQ-5D	EuroQoL 5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAS	Full-analysis set
FDA	Food and Drug Administration
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
IA2	Second Interim-Analysis

Abbreviation	Definition
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
INV	Investigator evaluation
IPCW	Inverse probability of censoring weighted
irAEs	Immune-related AEs
IRO	Integrated radiology and oncology analysis (central review)
IRC	independent review committee
irRC	Immune-related response criteria
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IV	Intravenous
IVRS/IXRS	Interactive Voice Response System
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
mAb	Monoclonal Antibody
MEK	Mitogen-activated protein kinase
MHRA	Medicines and Healthcare Products Regulatory Agency
MK-3475	Pembrolizumab - Keytruda®
MSD	Merck Sharp and Dohme Ltd
NCCN	National Comprehensive Cancer Network
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
ORR	overall response rate
OS	overall survival
PAS	Patient Access Scheme
PBM	Preference-Based Measure
PD	Progressive Disease
PD-1	Programmed Death 1 protein
PD-L1	Programmed cell Death 1 ligand
PFR	Progression-free rate
PFS	Progression free survival
PIM	Promising Innovative Medicines
PK	Pharmacokinetics
PR	Partial response
PRO	Patient Reported Outcomes
PSS	Personal Social Services
PT	Preferred Term
QALY(s)	Quality-Adjusted Life Year(s)
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank-preserving structural failure time
RR	Response rate
SACT	Systemic Anti- Cancer Therapy
ScHARR	School of Health and Related Research
SD	Stable Disease
SD	Standard Deviation
SE	Standard Error
SFU	Survival follow-up
SmPC	Summary of Product Characteristics
SMR	Society of Melanoma Research
SOC	Standard of Care
SOC	System Organ Class
STA	Single Technology Appraisal
TIC	Treatment of Investigator choice
TNM	Tumour, Node, and Metastases
TTO	Time Trade Off
ULN	Upper limit of normal

Abbreviation	Definition
UV	Ultraviolet
VAS	Visual Analogue Scale
VAT	Value-Added Tax
RR	Target Response Rate

1 Executive summary

Brief background to the condition

Melanoma is a type of skin cancer originating in the pigment-producing melanocytes, found between the epidermis and the dermis. It is a heterogeneous disease reflected by its complex pathobiology. Melanoma disproportionately affects a younger population compared to other cancers and therefore has significant impact for patients, family and wider society.

Over the past three years, three new drugs (ipilimumab,[2;3] vemurafenib and dabrafenib) have been approved by NICE for the treatment of metastatic melanoma. Yet the condition still has a dismal prognosis, with a 5-year overall survival (OS) rate of between 20% and 34% for stage IIIc patients, and between 5% and 22% for patients with stage IV disease.[4]

The clinical care pathway for patients with stage IIIc or stage IV (unresectable or metastatic) melanoma is currently determined by the tumour genotype, with patients identified as $BRAF^{V600}$ mutation positive being eligible to receive first-line treatment with either a BRAF inhibitor or with ipilimumab. For patient with $BRAF^{V600}$ wild type status, ipilimumab is currently a recommended first-line treatment option. Dacarbazine, although offering no survival benefit, is sometimes used when immunotherapy or targeted therapies are not suitable, or after they have failed.

For patients with $BRAF^{V600}$ mutation positive melanoma, the newer recommended chemotherapy agents vemurafenib and dabrafenib have demonstrated a modest effect on progression-free survival (PFS) and OS. Unfortunately though, the majority of these patients will eventually relapse, partly due to the ability of melanoma tumors to develop resistance with prolonged treatment.[5-8] The immuno-oncology agent ipilimumab, has a marked benefit for a small proportion of patients,[9] whether $BRAF^{V600}$ mutation positive or wild type, although with a high immune-related AE[10;11] profile. Consequently most patients continue to face a remarkably poor prognosis.[5-7]

With this submission, pembrolizumab is proposed to be used as a first- or second-line treatment option for adult patients with advanced melanoma who are naïve to treatment with ipilimumab. Therefore, pembrolizumab is expected to displace the use of ipilimumab and BRAF inhibitors (the later only used among $BRAF^{V600}$ mutation-positive patients) to further subsequent lines of treatment for patients experiencing confirmed disease progression. The proposed positioning of pembrolizumab in the treatment pathway is particularly relevant for patients who are $BRAF^{V600}$ wild-type, who currently have limited treatment options, with only ipilimumab recommended for use by NICE. $BRAF^{V600}$ mutation positive patients currently

have access to vemurafenib and dabrafenib as additional treatment options. Consequently, the use of pembrolizumab reflects a step change in the management of patients with unresectable or metastatic melanoma.

1.1 Statement of decision problem

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	People with advanced (unresectable stage III or stage IV) melanoma previously untreated with ipilimumab	Adults with unresectable or metastatic melanoma previously untreated with ipilimumab	The product label will cover a broader indication than the final scope, encompassing both patients who have been and have not been treated with ipilimumab.
Intervention	Pembrolizumab	Pembrolizumab	In line with NICE final scope
Comparator (s)	• Dacarbazine • Ipilimumab • Vemurafenib (for people with $BRAF^{V600}$ mutation-positive disease) • Dabrafenib (for people with $BRAF^{V600}$ mutation-positive disease)	• Vemurafenib (for people with $BRAF^{V600}$ mutation-positive disease) • Dabrafenib (for people with $BRAF^{V600}$ mutation-positive disease) • Ipilimumab	Given the recent positive NICE guidance for ipilimumab, vemurafenib and dabrafenib (the later for $BRAF^{V600}$ mutation positive patients) in the first line setting, Merck Sharp & Dohme Ltd. (MSD) MSD believe it is inappropriate for dacarbazine to be listed as a comparator when considering the population of interest. Additionally, MSD has consulted widely on the role of dacarbazine and other chemotherapeutic agents and there is unanimity in placing them in the position of palliation as part of BSC. This position is supported by the following: • There are no RCTs demonstrating an improvement in survival with dacarbazine relative to BSC / any other control agent. Dacarbazine is mostly used in a palliative setting outside of

			clinical trials.[12] • In a prospective study setting, no clear survival benefit was apparent for polychemotherapy (including dacarbazine) in addition to BSC compared with BSC alone in patients with advanced metastatic melanoma.[13] • Additionally, no other conventional cytotoxic chemotherapies (as either single agents or combinations) have demonstrated superiority to single agent dacarbazine in the treatment of melanoma in randomized controlled trials. The only placebo controlled RCT in patients with metastatic malignant pre-treated[14] failed to demonstrate any benefit with lenalidomide chemotherapy treatment in terms of tumour response, time to progression, or overall survival.
Outcomes	The outcome measures to be considered include: • PFS • OS • response rate (RR) • adverse effects of treatment • health-related quality of life (HRQoL)	The outcome measures to be considered include: • PFS • OS • response rate (RR) • adverse effects of treatment • health-related quality of life (HRQoL)	In line with NICE final scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services	• The cost-effectiveness will be expressed in terms of an incremental cost per quality-adjusted life year (QALY) • The time horizon considered will be 30 years • Costs will be considered from an NHS and PSS perspective • A range of potential PAS discounts for ipilimumab, vemurafenib and dabrafenib (in 5% increments) will be considered as part of the analyses to	In line with NICE final scope

	perspective. The availability of any patient access schemes for the comparator technologies should be taken into account.	reflect the confidential patient access schemes agreed by the manufacturers of these therapies.	
Subgroups to be considered	None	None	In line with NICE final scope
Special considerations including issues related to equity or equality	None	None	In line with NICE final scope

1.2 Description of the technology being appraised

The technology being appraised is described in Table 2 below:

Table 2: Technology being appraised

UK approved name and brand name	KEYTRUDA® (pembrolizumab)
Marketing authorisation/CE mark status	The Committee for Medicinal Products for Human Use (CHMP) has issued a positive opinion on KEYTRUDA for the treatment of advanced melanoma.[15] Marketing authorisation is expected in July 2015.
Indications and any restriction(s) as described in the summary of product characteristics	Indication to which this submission relates: KEYTRUDA is indicated for the treatment of unresectable or metastatic melanoma in adults *NB: This NICE submission indication covers a sub-population of the licence indication, namely advanced melanoma patients previously untreated with ipilimumab.* *In April 2015, MSD made an STA submission to NICE for the other sub-population covered by the licensed indication, namely for the treatment of unresectable, metastatic melanoma after progression with ipilimumab (ID760).*
Method of administration and dosage	2 mg/kg every three weeks (Q3W); intravenous (IV) infusion.

Pembrolizumab is a potent and highly selective humanised monoclonal antibody (mAb) of the IgG4/kappa isotype. It acts on the Programmed Death 1 protein (PD-1) immune-checkpoint receptor pathway, by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells. This in turn allows reactivation of both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumor immunity.

Pembrolizumab is currently under review by the European Medicines Agency (EMA). It received CHMP positive opinion on 21st May 2015[15] and the licence is anticipated in July 2015. The licence indication will be "for the treatment of unresectable or metastatic melanoma in adults" whereas our submission is focused on the sub-population of "patients with advanced melanoma previously untreated with ipilimumab."

The route of administration for pembrolizumab is intravenous (IV) infusion, over a 30 minute period. The licensed dosage will be 2 mg/kg Q3W. Treatment with pembrolizumab continues until disease progression is confirmed or unacceptable toxicity, whichever occurs first. The

list price of pembrolizumab is £1,315 per 50 ml vial (incorporating PAS: [redacted]). Each vial contains 50 mg of pembrolizumab. After reconstitution, 1 mL of solution contains 25 mg of pembrolizumab.

The innovative nature of pembrolizumab was first recognised by the US Food and Drug Administration (FDA) in January 2013 by granting it Breakthrough Therapy Designation for advanced melanoma, based on the significance of the early study findings regarding tumour response, durability of response and the unmet medical need. In the UK, pembrolizumab became the first product to be approved under the MHRA's Early Access to Medicines Scheme (EAMS) in March 2015. Under this process, pembrolizumab was recognised as a medicine for the treatment of a life threatening or seriously debilitating condition, and although currently unlicensed, meets an unmet medical need and is likely to offer significant advantage over methods currently used in the UK.

1.3 Summary of the clinical effectiveness analysis

Clinical and safety evidence presented in this submission demonstrate that pembrolizumab is a valuable first- or second-line treatment option for patients with advanced melanoma, previously untreated with ipilimumab.

Results from the first interim-analysis (IA1) and the second interim-analysis (IA2) of KEYNOTE-006, a head-to-head randomised controlled trial (RCT) directly comparing the two immune checkpoint inhibitors pembrolizumab and ipilimumab, provide the main evidence base for this submission. Supportive clinical evidence is provided from the randomised 'Part D' of KEYNOTE-001, which compared two strengths of pembrolizumab (2 mg/kg Q3W and 10 mg/kg Q3W) in the same patient population (previously untreated with ipilimumab) as that considered in KEYNOTE-006, as well as the non-randomised 'Part B1' of KEYNOTE-001 which included both patients who had received prior treatment with ipilimumab in addition to those who were naïve to ipilimumab therapy.

The results from the first interim analysis (IA1) of KEYNOTE-006 demonstrate the significant improvement in PFS associated with pembrolizumab when directly compared to ipilimumab (HR = 0.58; p <0.00001). The PFS curves separate by the time of the first assessment (12 weeks), with the separation increasing thereafter, reflected by a 6-month PFS rate of 46.4% in the pembrolizumab 10 mg/kg Q3W arm compared to 26.5% in the ipilimumab arm. The improvements in PFS associated with pembrolizumab were supported by a significantly higher confirmed ORR of approximately 3 fold (see section 4.7).

The OS results from the second interim-analysis (IA2) of KEYNOTE-006 show that pembrolizumab is associated with a statistically significant and clinically meaningful survival benefit when compared with ipilimumab in the population of interest (hazard ratio (HR) = 0.69 [p=0.00358] in the pembrolizumab 10 mg/kg Q3W arm over the ipilimumab arm, favouring pembrolizumab), with 12 month survival rates improved by 10% for subjects in the pembrolizumab arm compared to the ipilimumab arm.

Given that pembrolizumab met the pre-specified efficacy boundaries for both PFS and OS at IA2, the Data Monitoring Committee (DMC) recommended that KEYNOTE-006 should be stopped early for efficacy and the results unblinded, in addition to recommending that pembrolizumab be made available to the subjects with progressed disease (PD) that had been on the ipilimumab arm.

KEYNOTE-006 assessed two different dosing schedules (Q2W and Q3W) of the 10 mg/kg dose of pembrolizumab compared with ipilimumab. Although comparative data for the licensed dose of pembrolizumab (2 mg/kg) versus ipilimumab in an ipilimumab-naïve advanced melanoma patient population is unavailable from KEYNOTE-006, direct comparative evidence between the 2 mg/kg and 10 mg/kg doses of pembrolizumab is available from Part D of KEYNOTE-001 which relates to the same patient population of interest. The results of KEYNOTE-001 show comparable efficacy between both pembrolizumab doses for the endpoints of ORR, PFS and OS. The results from KEYNOTE-006 serve to corroborate that the difference in dosing regimens (Q2W vs. Q3W) makes no meaningful difference in terms of efficacy outcomes (see section 4.7).

The current evidence base does not provide direct comparative evidence between pembrolizumab and BRAF inhibitors (vemurafenib and dabrafenib). The results of the network meta-analysis (NMA) included in this submission demonstrate that pembrolizumab has at least comparable efficacy as the BRAF inhibitors among $BRAF^{V600}$ mutation positive patients without a history of systemic treatment, and based on extrapolation, pembrolizumab may have an advantage after 1 year of follow-up (see section 4.10).

The safety profile of pembrolizumab has been shown to be favourable compared with ipilimumab. No unexpected safety concerns occurred in KEYNOTE-006 and despite exposure to treatment being approximately 3 times longer with pembrolizumab as with ipilimumab at the time of data cut-off for analysis of AEs, the incidence of grade 3 to 5 events attributed to treatment was lower with pembrolizumab than with ipilimumab, as was the incidence of permanent discontinuation for an AE. Adjusted analyses which were

conducted to account for the 3-fold longer exposure to treatment in the pembrolizumab arms versus the ipilimumab arm also showed fewer AEs in pembrolizumab subjects (Section 4.12; Appendix 14). The frequency of high-grade immune related AEs (irAEs), serious irAEs and irAEs leading to discontinuation was approximately 2-fold higher for ipilimumab-treated subjects versus pembrolizumab-treated subjects.

The evidence presented in this submission validates the clinical superiority of pembrolizumab compared to ipilimumab in terms of efficacy and safety. Pembrolizumab has a statistically significant and clinically meaningful survival benefit versus ipilimumab, and therefore provides a valuable new first- or second-line treatment option in a population of patients with advanced melanoma.

1.4 Summary of the cost-effectiveness analysis

The cost-effectiveness of pembrolizumab was assessed against ipilimumab in $BRAF^{V600}$ wild type patients, and against ipilimumab, vemurafenib and dabrafenib in patients with $BRAF^{V600}$ positive mutation. Cost-effectiveness was evaluated through the development of a three-state partitioned survival model. This model considered PFS, post-progression and death, in line with previous HTAs concerning advanced melanoma (see section 5.2).[2;3;16;17] The model projected health outcomes (i.e. OS and PFS) to estimate patients' health-related quality of life (HRQoL) and costs. Quality-adjusted life years (QALYs) were estimated by using time-to-death utilities derived from EQ-5D data, in line with previous NICE submissions.[3] Clinical and economic outcomes were projected over a 30-year time horizon to cover the anticipated lifetime of the target population initiating first line or second line therapy.

The main clinical evidence used to populate the pembrolizumab and ipilimumab arms in the short term was the KEYNOTE-006 trial.

PFS and OS for pembrolizumab and ipilimumab were modelled during the first year using the KEYNOTE-006 KM data. For the longer term, OS was extrapolated using the published long term data for ipilimumab from the treatment-naïve cohort[9] and implementing conditional survival rates (see section 5.3.3). This approach was validated by the results of the Phase III, KEYNOTE-006 trial[18] and confirmed by melanoma clinical experts. In order to project the outcomes of vemurafenib and dabrafenib in the long- term, trial data from these treatments was utilised, followed by the use of time-dependent monthly risks as used in previous NICE submissions.[16;17] In sensitivity analyses, alternative scenarios were modelled for both

pembrolizumab and its comparators, making use of other available data sources external to the KEYNOTE-006 trial.

Section 5 details the development of the de novo economic model for pembrolizumab, with Table 3 and Table 4 below presenting the results for patients with $BRAF^{V600}$ wild type and $BRAF^{V600}$ positive mutations, respectively.

Independent of patients' BRAF status, the model estimates that patients treated with pembrolizumab gain 0.71 additional years (and 0.44 additional QALYS), compared to ipilimumab. In the base case analysis, pembrolizumab dominates ipilimumab, since it results in higher QALYs at a lower average cost per patient (with an average cost saving per patient of 21,185 with pembrolizumab).

In patients with a $BRAF^{v600}$ positive mutation, the model estimates that patients treated with pembrolizumab gain 2.34 additional life years (and 1.40 additional QALYs) compared to vemurafenib, and 1.67 additional life years (and 0.97 additional QALYs) compared to dabrafenib. Both pembrolizumab and dabrafenib dominate vemurafenib (with an average cost saving per patient of £6,695 with pembrolizumab). The corresponding ICER for pembrolizumab compared to dabrafenib is £5,852.

The key driver of the cost-effectiveness results is the improved survival seen with pembrolizumab. There is a larger proportion of patients surviving in the long term, beyond what would be expected with ipilimumab or BRAF inhibitors.

The probabilities of pembrolizumab being the most cost-effective treatment at thresholds of £20,000 and £30,000 per gained QALY are 89.9% and 90.5%, respectively, in $BRAF^{V600}$ wild type patients, and 80.1% and 86.4%, respectively, in $BRAF^{V600}$ mutation positive patients. When a threshold of £50,000 per additional QALY is considered, these probabilities increase to 91.6% among $BRAF^{V600}$ wild type patients and 90.1% among $BRAF^{V600}$ mutation positive patients.

Pembrolizumab represents a step change in the treatment of unresectable or metastatic melanoma as one of the first of a new class of immuno-oncology agents for use in patients with metastatic melanoma. Clinicians are confident that the availability of these newer agents, with their greater efficacy, will displace ipilimumab or BRAF inhibitors to second- or third-line.

Table 3: Incremental cost-effectiveness results for BRAF^{V600} wild type patients

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)	Incremental analysis
Pembrolizumab	£76,689	5.08	3.14	-	-	-	-	-
Ipilimumab	£97,873	4.37	2.69	£21,185	-0.71	-0.44	Dominated	Dominated
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years								

Table 4: Incremental cost-effectiveness results for BRAF^{V600} mutation positive patients

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)	Incremental analysis
Dabrafenib	£71,029	3.41	2.17	-	-	-	-	
Pembrolizumab	£76,689	5.08	3.14	£5,660	1.67	0.97	£5,852	£5,852
Vemurafenib	£83,384	2.74	1.73	£6,695	-2.34	-1.40	Dominated	Dominated
Ipilimumab	£97,873	4.37	2.69	£21,185	-0.71	-0.44	£51,336	Dominated
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years								

CONCLUSION

Pembrolizumab is an immunotherapy with a novel and innovative mode of action that offers a step change in the management of patients with advanced melanoma. Pembrolizumab significantly improves PFS and OS compared with currently recommended first-line therapies (i.e. ipilimumab and BRAF inhibitors, the latter only recommended to be used for the treatment of $BRAF^{V600}$ mutation positive patients). Pembrolizumab is a well-tolerated drug with fewer high-grade toxic events than the other available drugs. Pembrolizumab-induced immune-related adverse events (irAEs) are usually mild and easily manageable. Pembrolizumab is a highly cost-effective therapeutic option when compared to recommended first-line therapies, resulting in higher QALYs and lower costs when compared to ipilimumab and vemurafenib (as shown by the results of the de novo cost-effectiveness model). The availability of pembrolizumab for the treatment of patients with advanced (unresectable stage IIIc or stage IV) melanoma previously untreated with ipilimumab in England will represent a step-change in the treatment options available and will provide patients and clinicians with a transformative new treatment option.

2 The technology

2.1 Description of the technology

Brand name: KEYTRUDA®

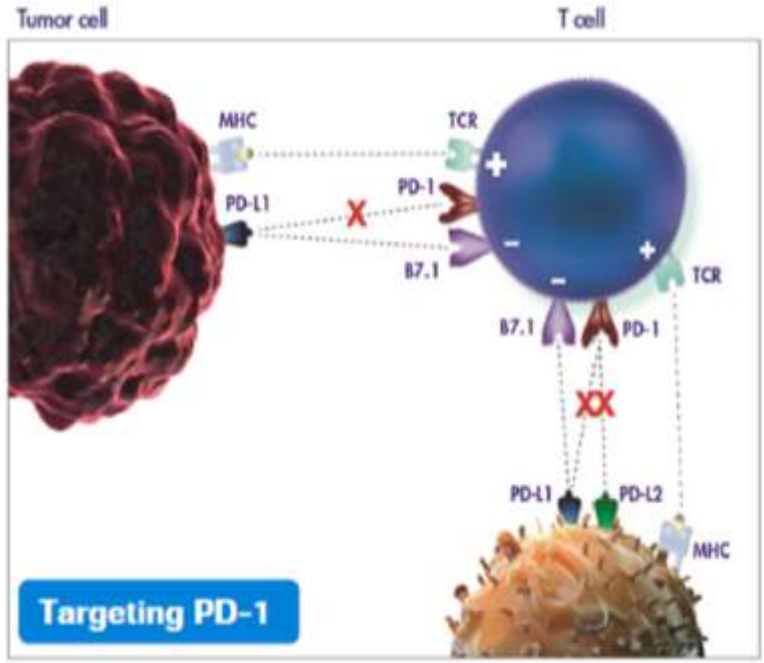
Generic name: pembrolizumab

Therapeutic class: Anticipated BNF Category "Other immunomodulating drugs" (08.02.04).[19]

Brief overview of mechanism of action:

Programmed death 1 protein (PD-1) is an immune-checkpoint receptor that is expressed on antigen-presenting T cells. PD-1 acts to initiate downstream signalling, which in turn inhibits the proliferation of T cells as well as cytokine release and cytotoxicity.[20] The PD-1 ligands, PD-L1 and PD-L2, are frequently upregulated on the surface of many tumour cell surfaces.[21]

Figure 1: Pembrolizumab – mode of action



Pembrolizumab (Keytruda®) is a potent and highly selective humanised monoclonal antibody (mAb) of the IgG4/kappa isotype.[20] designed to exert dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells (Figure 1). By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the

PD-1 pathway-mediated inhibition of the immune response, and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumor immunity (Figure 1).

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 Current UK regulatory status

- Application submitted: June 2014
- CHMP Opinion issued on 21st May 2015[15]
- Estimated date of Marketing Authorization: late July 2015

2.2.2 Indication in the UK

The licence indication in the UK will be as follows: "*KEYTRUDA is indicated for the treatment of unresectable or metastatic melanoma in adults*".

2.2.3 Anticipated restrictions or contraindications that are likely to be included in the draft summary of product characteristics (SmPC)

Please see Appendix 1.

2.2.4 Draft SmPC

The draft SmPC[15] has been included as an appendix – see Appendix 1. Please note this draft SmPC will be subject to change as the regulatory review progresses and therefore the final version may differ compared to the one presented in Appendix 1.

2.2.5 Draft EMA assessment report

The draft EMA assessment report is currently unavailable and is anticipated to be available in the first half of June 2015. It will be forwarded on receipt.

2.2.6 Summary of the main issues discussed by the regulatory authorities

See section 2.2.5 above.

2.2.7 Anticipated date of availability in the UK

Pembrolizumab is already available in the UK under the Early Access to Medicines Scheme (EAMS) – see section 2.5.

The anticipated commercial launch date following regulatory approval is July 2015

2.2.8 Details of regulatory approval outside of the UK

To date, pembrolizumab has received regulatory approval in the following countries on the dates provided below:

- USA: 04 September 2014
- Israel: 15 February 2015
- Macau: 12 February 2015
- Korea: 20 March 2015
- UAE: conditional approval: 25 March 2015
- Australia: 16 April 2015

In Israel and Australia Keytruda® is approved for the treatment of patients with unresectable or metastatic melanoma.

In the remaining countries identified above, the approved indication is *"KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if $BRAF^{V600}$ mutation positive, a BRAF inhibitor".*

2.2.9 Other health technology assessments in the UK

There is an ongoing NICE STA of pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab (ID760).[22]

MSD will be making a submission to the Scottish Medicines Consortium (SMC) in June 2015, subdivided into 'previously-treated with ipilimumab' and 'previously-untreated' patient populations.

2.3 Administration and costs of the technology

Table 5: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Powder for concentrate for solution for infusion	Draft SmPC[15] (see Appendix 1)
Acquisition cost (excluding VAT) *	List price: 50mg vial = £1,315 A PAS is currently under discussion with the Department of Health. The NHS acquisition cost (excl. VAT) is: 50mg vial = [redacted]	Pending confirmation with Department of Health
Method of administration	Intravenous infusion	Draft SmPC[15] (see Appendix 1)
Doses	Induction dose: 2mg/kg every 3 weeks	Draft SmPC[15] (see Appendix 1)
Dosing frequency	Induction: 2mg/kg every 3 weeks until disease progression is confirmed or unacceptable toxicities	Draft SmPC[15] (see Appendix 1)
Average length of a course of treatment	The mean treatment duration reported in the KEYNOTE-006 clinical trial for patients treated with pembrolizumab 10mg/Q3W is 151 days, estimated at approximately 7.19 cycles (21.57 weeks).	Clinical trial – KEYNOTE-006[23]
Average cost of a course of treatment	Based on a mean treatment duration of 7.19 cycles (see above) the average cost per a course of treatment is £34,613.([redacted] with PAS)	Clinical trial –KEYNOTE-006[23]
Anticipated average interval between courses of treatments	Treatment regimen is continuous until disease progression is confirmed or unacceptable toxicity leading to discontinuation	Clinical trial – KEYNOTE-006[23]
Anticipated number of repeat courses of treatments	Repeated treatment is not anticipated	Draft SmPC[15] (see Appendix 1)
Dose adjustments	No dose adjustment is expected	Draft SmPC[15] (see Appendix 1)
Anticipated care setting	Pembrolizumab is anticipated to be administered in hospital setting only.	
* 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

2.4.1 Additional tests or investigations needed

No additional tests, investigations or monitoring of patients will be required during use of pembrolizumab that is over and above that conducted within usual clinical practice. No diagnostic test is required to identify the population for whom pembrolizumab is indicated and no particular administration for the technology is required.

2.4.2 Main resource use to the NHS associated with the technology being appraised

Pembrolizumab is administered until disease progression is confirmed or unacceptable toxicity. The main resource use to the NHS associated with the use of pembrolizumab is therefore expected to be related to the management of patients in the pre-progression period. Pembrolizumab has shown a significant improvement in PFS and OS (see section 4.7) which may significantly increase resource use to the NHS.

The administration of pembrolizumab will take place in a secondary care (i.e. hospital setting) with no inpatient stay required. Patients will receive pembrolizumab as an outpatient on a 3-weekly cycle, with a duration of administration of 30 minutes per infusion.

2.4.3 Additional infrastructure in the NHS

Pembrolizumab is not anticipated to require any additional infrastructure in the NHS to be put in place.

2.4.4 Extent that the technology will affect patient monitoring compared with established clinical practice in England

Pembrolizumab is expected to provide durable benefit for a proportion of patients treated. These patients can be anticipated to receive ongoing follow-up including scanning as long as they do not show signs of progression.

2.4.5 Concomitant therapies administered with the technology

No concomitant therapies are required.

2.5 Innovation

2.5.1 State whether and how the technology is a 'step-change' in the management of the condition

The treatment pathway for melanoma has evolved over the last 3 years, given the positive NICE guidance issued for ipilimumab[2;3], vemurafenib[24] and dabrafenib[17].

Ipilimumab has improved survival in both previously treated and untreated unresectable or metastatic melanoma patients, with a plateau for survival of about 20% in both settings starting at 3 years and extending up to 10 years in some patients[9]. BRAF inhibitors have demonstrated impressive initial responses in advanced melanoma, but often only allow for transient disease control that is inevitably followed by patients developing resistant disease resulting in disease progression by 6-7 months.[25]

Single-agent dacarbazine is also approved for the treatment of advanced melanoma, although its use is declining rapidly in the UK. This is because it is associated with a low level of clinical activity, even in treatment-naïve patients. In nine of the largest randomised controlled trials conducted between 1999 to 2012 using single-agent dacarbazine as the control arm with nearly 1,700 patients randomized to single-agent dacarbazine, the response rates for dacarbazine ranged from 6.0-12.1%, and the median duration of response ranged from 6.9-11.2 months in the small fraction of patients who responded to treatment.[5;26-33]

The overall clinical outlook for metastatic or unresectable melanoma patients remains bleak in spite of the recent progress noted above.

Pembrolizumab, the first PD-1 to be reviewed by NICE, will increase the range of treatment options and is expected to provide a durable response for a significant proportion of patients treated. Consequently, pembrolizumab is a step-change in the management of patients with advanced melanoma.

The innovative nature of pembrolizumab was recognised by the US Food and Drug Administration (FDA) in January 2013 by granting it Breakthrough Therapy Designation for advanced melanoma, based on the significance of the early study findings regarding tumour response, durability of response and the unmet medical need.

This was followed in September 2014, with the FDA granting accelerated approval to pembrolizumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if $BRAF^{V600}$ mutation positive, a BRAF inhibitor.[34]

In the UK, the MHRA launched EAMS in April 2014. The scheme is intended to provide access for patients to medicines for treatment of life threatening or seriously debilitating conditions that do not yet have a marketing authorisation but meet an unmet medical need.

Assessment under EAMS involves a two stage assessment process, conducted by the MHRA, to determine whether a medicine meets specific pre-defined criteria (including:

whether the condition intended for treatment is life threatening or seriously debilitating; whether there is a high unmet need, i.e. there are no methods available or existing methods have serious limitations; and whether the medicinal product is likely to offer significant advantage over methods currently used in the UK).[35]

Pembrolizumab received Promising Innovative Medicines (PIM) designation (EAMS Step 1) in October 2014, and in March 2015 a positive Scientific Opinion was issued (MHRA EAMS number 00025/0626),[36] for use in the treatment of unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care agents including ipilimumab, and when indicated a V-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor or mitogen activated protein kinase (MEK) enzyme inhibitor (EAMS Step 2).

Pembrolizumab is the first medicine to be approved under EAMS, and validates MSD's position that pembrolizumab should be considered innovative in its potential to make a significant and substantial impact on health-related benefits. Approval under EAMS will help ensure continuity and equity of patient access across the UK to this drug prior to UK Marketing Authorisation. Availability of pembrolizumab under EAMS follows previous access to the drug under MSD UK's earlier Expanded Access Programme (EAP), in which eligible patients with advanced melanoma who had been previously treated with ipilimumab and, if indicated, a BRAF inhibitor were able to access pembrolizumab since Spring 2014.

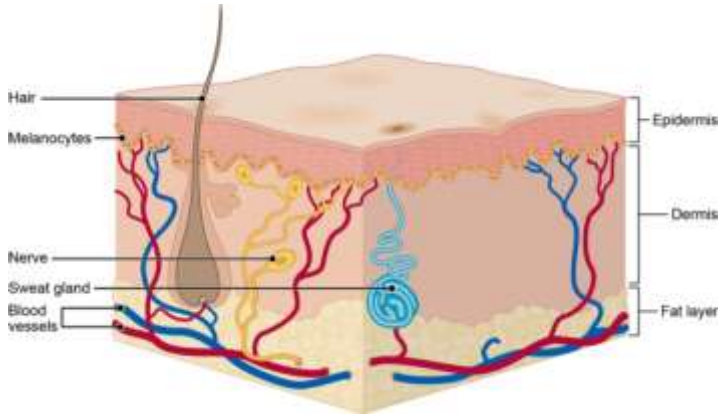
Following the approval of pembrolizumab under EAMS, NICE is appraising the product as a priority. NICE has agreed that their guidance will be implemented 30 days after final guidance is published, at which point the funding of pembrolizumab would switch to routine commissioning by NHS England (NHSE).

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

3.1 Brief overview of the disease/condition for which the technology is being used

Melanoma is a type of skin cancer originating in the pigment-producing melanocytes, which are found between the outer layer of the skin (the epidermis) and the layer beneath (the dermis; see Figure 2). Melanocytes produce melanin, a pigment that helps to protect the skin against damage caused by ultraviolet (UV) light from the sun.[2;37]

Figure 2: The structure of the skin. [Adapted from Cancer Research UK (2014a)].[2;37]



The darker a person's skin, the more active their melanocytes are at producing melanin. Additionally, exposure of skin to the sun during an individual's lifetime causes melanocytes to increase melanin production, and the pigment is then transferred to other skin cells to help protect them against ultraviolet (UV) damage from the sun. Melanin not only colours (or tans) the skin, but also produces moles (nevi).[2;37]

Melanocytes can become cancerous as a result of unrepaired DNA damage and/or other genetic alterations. There are a number of genetic and environmental factors that increase the risk of melanoma, including: acute exposure to sunlight and UV radiation; having a high number of moles (nevi); being very fair skinned (especially with fair or red hair); family history; lowered immunity (e.g., due to human immunodeficiency virus/AIDS or due to organ transplant); age; being male, having a history of previous melanoma; and lighter eye colour.[2;37-39]

Melanoma is a heterogeneous disease reflected by its complex pathobiology. Cell cycle dysregulation in melanoma represents one of the most important pathogenetic mechanisms

for its oncogenesis, resulting in uncontrolled cellular proliferation.[40] There are several types of melanoma. Superficial spreading melanoma, nodular melanoma, and lentigo maligna melanomas comprise 90% of all diagnosed malignant melanomas. The other types are rarer and together take account of the remaining 10%.[41]

Several classifications have been developed to describe how deeply a melanoma has grown into the skin and whether it has spread to regional lymph nodes or distant (metastatic) sites at the time of initial diagnosis.[42;43] The Tumour, Node, and Metastases (TNM) staging represents the cornerstone for the management of melanoma. This staging system summarizes information about the thickness of the melanoma, the extent of any spread to regional lymph nodes or other parts of the body and the presence of skin ulceration.[44]

In stage 0 melanoma (in situ melanoma), the abnormal melanocytes have not started to spread into deeper layers. In stages I and II melanoma, an invasive cancer has formed but there is no spread to lymph nodes or distant sites. In stage III melanoma, the melanoma has spread to the lymph nodes or lymphatic channels and it may or may not be ulcerated. In stage IV melanoma, the cancer has spread elsewhere in the body, with the brain, lung, liver, the distant lymph nodes and other areas of the skin being the most common places of metastasis.[44]

3.2 Effects of the disease/condition on patients, carers and society

Melanoma disproportionately affects a younger population than other cancers, resulting in a significant impact for patients, family and wider society. Approximately 27% of cases diagnosed with melanoma in the UK between 2009 and 2011 were in patients aged less than 50 years, while 24% of cases affected patients aged 75 and over. This compares with 11% and 36%, respectively, when considering all cancers combined (excluding non-melanoma skin cancer).[45] Given its life-threatening nature, a diagnosis of metastatic melanoma strongly impacts patients' life expectancy and health related quality of life (HRQoL), including psychological functioning. The emotional impact can be long lasting and profound, with the most common reactions being anxiety, depression, vulnerability and a deterioration in patients' quality of life.[46-50] Although differences in emotional distress do not seem to differ by stage of melanoma, women report greater distress than men.[51] Increased levels of impairment have been associated with poor recovery, an increase in morbidity and disease progression.[52] While on treatment, patients with metastatic melanoma incur travel costs and costs associated with lost earnings from time off work.[53] They also experience bothersome disease-related symptoms, including fatigue, insomnia, and appetite loss, and a

significant, progressive decrease in functioning over time, including physical, role, and social functioning.[47;54]

The purpose of treatment for patients with unresectable or metastatic melanoma is to enable patients to resume everyday tasks and activities (by slowing down the progression of disease). Although some progress has been made in the treatment of metastatic melanoma over recent years with the approval of ipilimumab (Yervoy®), the targeted BRAF kinase inhibitors, including vemurafenib (Zelboraf®)[5] and dabrafenib (Tafinlar®),[6] and the MEK inhibitor trametinib (Mekinist),[10] the prognosis of metastatic melanoma remains dismal, with a 5 year overall survival of approximately 20% in the group of patients that have been treated with ipilimumab.[9]

Brain metastases are common among patients with metastatic melanoma (between 4 and 16% of patients with melanoma develop brain metastasis) and are associated with a poor prognosis, leading to significant morbidity, including neurologic, cognitive and emotional difficulties.[55;56]

At a societal level, metastatic melanoma imposes a substantial financial cost to both the health care system and the wider economy. The total societal cost associated with malignant melanoma in England in 2002 was estimated as £138 million. From this figure, 14.7% related to costs incurred by the NHS for the management of these patients while the remainder comprised costs borne by patients (2.6%), lost working days due to morbidity (15.1%) and lost working life years due to deaths (67.6%).[53] Premature morbidity and mortality due to metastatic melanoma also have an impact on economic productivity; premature mortality results in a substantial number of years of life lost. A study conducted in East Anglia estimated that melanoma resulted in an average of 15.1 years lost per patient. For metastatic melanoma this figure was estimated as 23.2 years, positioning this condition as one of the leading causes of lost years of life due to cancer.[57] This serves to further emphasise the need for continued funding of research for this disease.

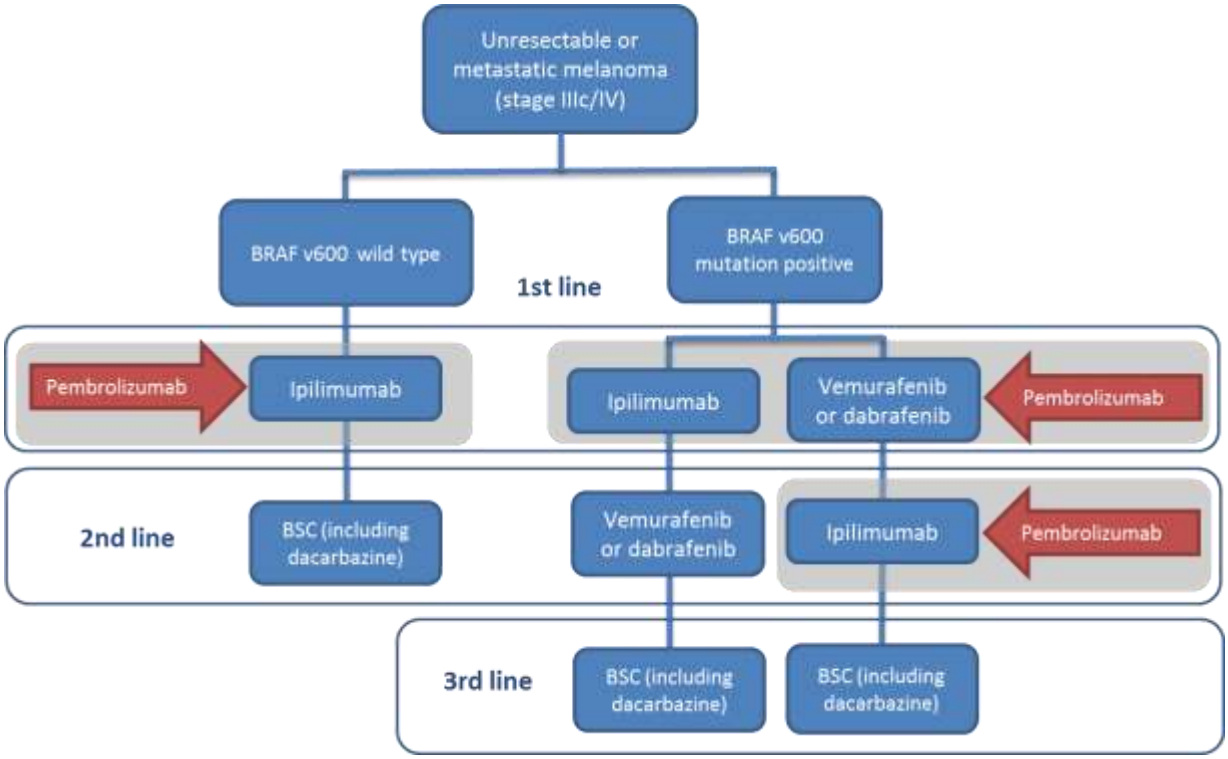
3.3 Clinical pathway of care showing the context of the proposed use of the technology

The clinical care pathway for patients with stage IIIc or stage IV (unresectable or metastatic) melanoma is determined by the tumour genotype. According to current NICE guidance, patients identified as $BRAF^{V600}$ mutation positive are eligible to receive first-line treatment with a BRAF inhibitor, either vemurafenib (Zelboraf®; Roche)[16] or dabrafenib (Tafinlar®; GSK),[17] or with ipilimumab (Yervoy®; BMS).[2] A BRAF inhibitor is more likely to be used as

the first-line option of choice for $BRAF^{V600}$ positive patients with rapid disease progression, given that it can take weeks to months to build a complete immune response against a tumour with ipilimumab.[58] In any case, no apparent detriment to the effectiveness of either agent has been observed when used sequentially (either ipilimumab first followed by a BRAF inhibitor or vice versa).[59] For patients with negative $BRAF^{V600}$ status (BRAF wild-type), ipilimumab is currently a recommended first-line treatment option.[2] Dacarbazine is to be considered when immunotherapy or targeted therapy are not suitable. Whilst most patients with $BRAF^{V600}$ positive mutations who receive BRAF inhibitors demonstrate an initial good response, it appears that most of these patients will eventually relapse, in part due to the ability of melanoma tumors to develop resistance with prolonged treatment), resulting in a remarkably poor prognosis for most patients.[5-8]. The first approved immunotherapy agent, ipilimumab, has a marked benefit for a small proportion of patients,[9] although with a high immune-related AE profile.[18] Consequently, there remains an unmet need, as most patients continue to face a remarkably poor prognosis.[5;6;60]

With this submission, pembrolizumab is proposed to be used as a first- or second-line treatment option for adult patients with advanced melanoma who are naïve to treatment with ipilimumab (as shown in Figure 3 below). Therefore, pembrolizumab is expected to displace the use of ipilimumab and BRAF inhibitors (the later only used among $BRAF^{V600}$ mutation-positive patients) to further subsequent lines of treatment for patients experiencing confirmed disease progression.

Figure 3: Treatment algorithm for unresectable or metastatic melanoma with proposed positioning for pembrolizumab



The proposed positioning of pembrolizumab in the treatment pathway is particularly relevant for patients who are $BRAF^{V600}$ wild-type, who currently have limited treatment options. For such patients, the only active treatment currently recommended by NICE and with a demonstrated OS benefit is ipilimumab, while $BRAF^{V600}$ mutation positive patients have access to vemurafenib and dabrafenib as additional active options with demonstrated improvement in OS at a class level.[2;16;17;61] As a consequence, the use of pembrolizumab reflects a step change in the management of patients with unresectable or metastatic melanoma.

3.4 Information about the life expectancy of people with the disease or condition in England and the source of the data

Melanoma is potentially curable when diagnosed at an early stage; however, among the different types of skin cancer, it has the greatest metastatic potential, with metastatic disease (stage IV) present in 1% of the patients at diagnosis.[45] Although some progress has been made in the treatment of metastatic melanoma over recent years, it still has a dismal prognosis, with a 5-year OS rate of between 20% and 34% for stage IIIc patients, and between 5% and 22% for patients with stage IV disease.[4]

The number of expected incident cases of malignant melanoma for 2015 in England is estimated to be 12,601 (see section 6), of whom 1,260 cases (10%) are expected to be stage IIIc and IV. The projected number of patients eligible for treatment with pembrolizumab in the next 5 years is presented in Table 6.

Table 6: Estimated patient numbers for England, 2015-2019

Year	2016	2017	2018	2019	2020
Incidence of Malignant Melanoma	13,040	13,500	13,970	14,460	14,970
Total stage IIIc and IV ipilimumab-naïve patients eligible for pembrolizumab in first-line	1,304	1,350	1,397	1,446	1,497

3.5 Details of relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being used

Details of relevant NICE guidance are provided below:

- In December 2012 NICE recommended the use of ipilimumab (Yervoy®, Bristol-Myers Squibb) as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, and vemurafenib (Zelboraf®, Roche) as a treatment option for $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma, each of them only if the manufacturers provide these treatments with the discounts agreed in the corresponding patient access schemes (PAS).[2;16]

- In July 2014 ipilimumab was further recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the PAS.[3]
- In October 2014 NICE recommended the use of dabrafenib (Tafinlar®, GSK), within its marketing authorisation, as an option for treating unresectable or metastatic $BRAF^{V600}$ mutation-positive melanoma only if the company provides dabrafenib with the discount agreed in the PAS.[17]

Additionally, guidance on the development of cancer services for people with skin tumours (including melanoma), focusing mainly on the organisation of services, was published by NICE in 2006.[62] At the time, non-surgical treatment options including dacarbazine and

interferon-α, were recommended. When the guidance was updated and published in October 2011, it mentioned the ongoing technology appraisals for ipilimumab and vemurafenib and provided reference to their corresponding key clinical trials.[63]

A NICE clinical guideline for the assessment and management of malignant melanoma is currently under consultation and is due for publication in July 2015.[61] The draft version of this clinical guideline states that genetic testing should be offered "*if targeted systemic therapy is a treatment option for stage 4 disease*". This is consistent with recommendations presented in several recently published NICE single technology appraisals of melanoma treatments:[2;3;16;17;61]

3.6 Details of other clinical guidelines and national policies

Details of other clinical guidelines and national policies are summarised below:

- National Comprehensive Cancer Network (NCCN) Melanoma Guidelines version 2.2015[64]
    - The most recent published guideline on Melanoma is the updated NCCN guideline, which now classifies pembrolizumab, along with nivolumab as a "preferred regimen". The guideline states that "….*there is consensus among the NCCN panel that both drugs have higher response rates and less toxicity than ipilimumab, and that both drugs should be included as options for first line treatment.*"
- European Society for Medical Oncology (ESMO). Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow up (2012)[65]
    - In these guidelines, ipilimumab was identified as an option for first- and second-line treatment for all patients and vemurafenib for the treatment of patients with BRAF-mutant melanoma, particularly in patients with symptomatic, bulky metastases given the faster onset of action and expected response. No recommendations regarding treatment sequencing for $BRAF^{V600}$ mutation positive metastatic melanoma were provided in the guidelines due to lack of data to guide decisions.
- British Association of Dermatologists. Revised UK guidelines for the management of cutaneous melanoma (2010)[66]
    - Since this update preceded the introduction of targeted therapies, dacarbazine was the recommended standard treatment option outside of clinical studies, with the acknowledgement that no survival benefits had been shown in patients with advanced melanoma.[67]

    - An updated European consensus-based multidisciplinary guideline was published in 2012, developed with the collaboration of multidisciplinary experts from the European Dermatology Forum, the European Association of Dermato-Oncology and the European Organization of Research and Treatment of Cancer. Although the guideline established that a treatment algorithm for stage IV melanoma could not be established at that time due to insufficient data, it stated that $BRAF^{V600}$ mutation positive patients should be offered treatment with BRAF inhibitors in the context of clinical trials while those experiencing progression on first-line treatment and with a health status expected to lead to at least 6 months of survival should be offered ipilimumab. Chemotherapy should be considered for $BRAF^{V600}$ wild-type patients and those $BRAF^{V600}$ mutation positive patients progressing after a BRAF inhibitor.
- Royal College of Physicians. The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines (2007)[68]
    - These concise guidelines cross-refer to the treatment recommendations published by the British Association of Dermatologists (see above).

3.7 Issues relating to current clinical practice, including variations or uncertainty about established practice

Clinical practice is constrained by current NICE guidance which continues to reflect that there is a role for dacarabazine in the active management of patients with metastatisc melanoma and we therefore excluded dacarbazine from the decision problem as a comparator (see Table 1).

3.8 Equality issues

We do not believe that there are any equity or equality issues.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Search strategy

A search strategy was developed to identify relevant studies for the technology. Further details are provided under the below subheadings.

4.1.2 Search strategy: description of the search strategy

A systematic literature search was conducted to identify randomised controlled trials (RCTs) that included pembrolizumab, in patients with unresectable or metastatic melanoma, previously untreated with ipilimumab (i.e. ipilimumab-naïve patients).

The following databases were searched from inception to 12 May 2015: Medline, EMBASE, Cochrane Central Register of Controlled Trials and Toxline.

In brief, the search strategies included terms related to the population, intervention, and study design of interest. With regards to population, search terms included skin tumour, skin neoplasms, melanoma, and skin cancer. In addition to the above mentioned database searches, Clinicaltrials.gov, the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), the Society of Melanoma Research (SMR) and the American Association for Cancer Research (AACR) conferences (over the past 2 years) were also searched to identify additional study information that had not yet been published in a peer-reviewed journal.

Full details of the search strategy used are provided in Appendix 2. The inclusion and exclusion criteria used to select studies are given in section 4.1.3.

4.1.3 Study selection

Description of the inclusion and exclusion selection criteria, language restrictions, and the study selection process

Two investigators working independently scanned all abstracts identified in the literature search. The same two investigators independently reviewed relevant abstracts in full-text. Discrepancies occurring between the studies selected by the two investigators were resolved by involving a third investigator and reaching consensus. The eligibility criteria used in the search strategy is provided in Table 7 below:

Table 7: Eligibility criteria used in the search strategy

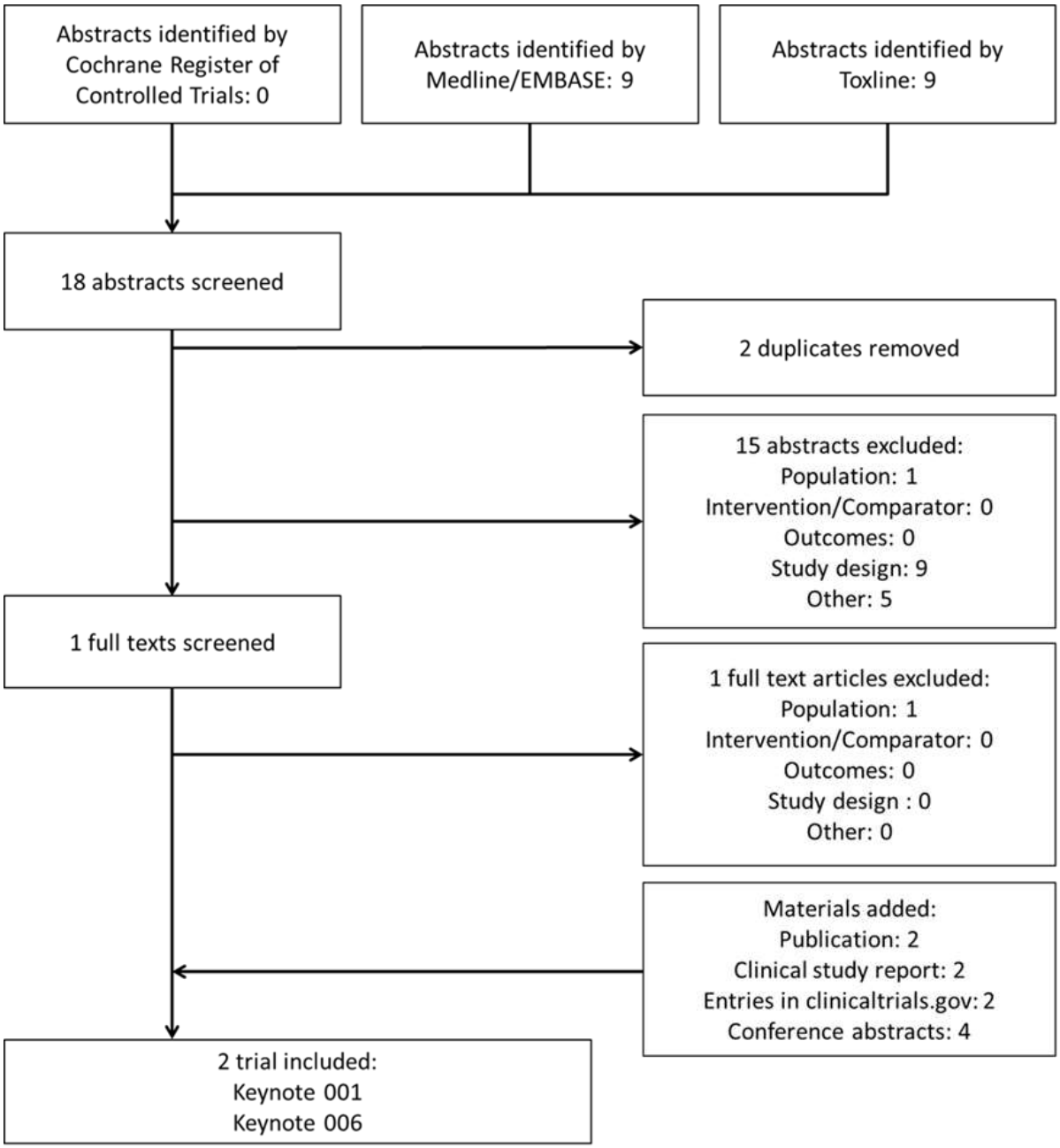
Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with unresectable stage III or IV melanoma, naïve to treatment with ipilimumab	Patients with non-cutaneous melanoma (i.e. ocular or mucosal melanoma) and with unknown primary site
Intervention	Pembrolizumab / MK-3475	Any other intervention
Comparators	The following treatments as monotherapy or as combination therapy* • Dacarbazine (DTIC) • Ipilimumab • Vemurafenib • Dabrafenib	Any other comparison
Outcomes	At least one of the following outcomes:** • Progression-free survival (PFS) • Overall survival (OS) • Overall response (OR)	Other efficacy and safety outcomes to be considered for analysis, but each study must include at least one of those presented to the left
Study design	Randomised controlled trials (RCTs)	Non-randomised clinical trials, prospective and retrospective observational studies, case studies
Language restrictions	Studies published in English language	Any other language

*DTIC – trade name for dacarbazine; *Relevant combination treatments needed to include at least 2 of the interventions listed; **Note: the scope of the review included extraction of safety outcomes, but for selection of relevant studies the focus was on efficacy outcomes*

4.1.4 Flow diagram of the numbers of studies included and excluded at each stage

The electronic searches yielded 18 abstracts concerning pembrolizumab. Of these abstracts, 2 duplicates were removed and 15 were excluded during abstract screening, which led to 1 article being included in the full text screening phase. Further details are provided in the below flow diagram (Figure 4):

Figure 4: Flow diagram of included and excluded publications



Note: KEYNOTE-006 data consists of one clinical study report,[23] one conference abstract,[1] one peer-reviewed publication[18] and one entry in clinicaltrials.gov[69]. KEYNOTE-001 (Part D) data consists of one clinical study report,[70] three conference abstracts,[71-73]one peer-reviewed publications,[74] and one entry in clinicaltrials.gov[75]

Execution of the search strategy and application of the inclusion/exclusion criteria resulted in 1 relevant RCT (KEYNOTE-006[1;18;23;69] which evaluated the primary treatment of interest, pembrolizumab, in population of patients previously untreated with ipilimumab (i.e. ipilimumab naive patients).The KEYNOTE-001 study[70-72;75;76] also relates to the population

covered by the decision problem, so was added post-hoc to the results of the systematic search, based on current available evidence.

4.1.5 Single study data drawn from multiple sources

KEYNOTE-006 data consists of one clinical study report,[23] one conference abstract,[1] one peer reviewed publication[18] and one entry in clinicaltrials.gov.[69]

KEYNOTE-001 data consists of one clinical study report,[70] three conference abstracts,[71-73] two peer-reviewed publications,[20;74] and one entry in clinicaltrials.gov[75]. Only Part D of KEYNOTE-001 is specifically focused on the population of relevance to the decision problem. Data and results focusing on Part D of KEYNOTE-001 are drawn from one clinical study report,[70] and one entry in clinicaltrials.gov.[75]

4.1.6 Complete reference list for excluded studies

A complete reference list for excluded studies has been provided in Appendix 3.

4.2 List of relevant randomised controlled trials

4.2.1 List of relevant RCTs involving the intervention of interest

Table 8: List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
KEYNOTE-006	• Histologically confirmed diagnosis of unresectable Stage III or metastatic melanoma not amenable to local therapy • Patients who have not received prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (first line) or who have received one prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (second line) are both eligible • Patients must have testing for a BRAF mutation prior to study entry. Patients with $BRAF^{V600}$ mutant melanoma may have received prior BRAF inhibitor therapy as first-line systemic therapy and be eligible for this study as second line treatment. At the discretion of the investigator, patients with $BRAF^{V600}$ mutant melanoma who have NOT received a BRAF inhibitor are also eligible for this study as first line treatment if they meet additional criteria (see section 4.3.1)	Pembrolizumab 10 mg/kg Q2W Pembrolizumab 10 mg/kg Q3W	Ipilimumab 3 mg/kg Q3W (total of 4 doses)	• CLINICAL STUDY REPORT – KEYNOTE-006[23] • Robert et al (2015) Pembrolizumab versus Ipilimumab in Advanced Melanoma *NEJM*[18] • Ribas et al (2015) KEYNOTE-006: Phase III Study of Pembrolizumab (MK-3475) versus Ipilimumab in Patients With Ipilimumab-Naive Advanced Melanoma *AACR*[1] • ClinicalTrials.gov reference: NCT01866319[69]
KEYNOTE-001 Part D	• Histological or cytological diagnosis of melanoma with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent. • Patients must be naive to ipilimumab and may not have received more than 2 prior systemic treatment regimens for treatment of melanoma. (*Part D represents patients, naïve to ipilimumab treatment and reflects the patient population included in KEYNOTE-006)	Pembrolizumab 2 mg/kg Q3W	Pembrolizumab 10 mg/kg Q3W	• CLINICAL STUDY REPORT – KEYNOTE-001[70] • ClinicalTrials.gov reference: NCT01295827[75]

Of the trials listed above, only KEYNOTE-006 compares the intervention (pembrolizumab) with a comparator of relevance to the decision problem (ipilimumab).

The currently available evidence base does not include any trials that evaluate pembrolizumab relative to the BRAF inhibitors (vemurafenib or dabrafenib) or BSC (including older chemotherapy agents such as dacarbazine) among patients naïve to treatment with ipilimumab. However, an RCT comparing lenalidomide plus BSC and BSC alone as second-line treatment among patients not exposed to ipilimumab suggests that chemotherapy in addition to BSC, after failure of first-line systemic treatment, demonstrates no benefit in terms of tumour response, time to progression, or overall survival.[14] Similarly, a non-randomised prospective study did not find that chemotherapy has any benefit over BSC in patients with advanced metastatic melanoma.[13] Dacarbazine is mostly used in a palliative setting outside of clinical trials[12] and there are no RCTs demonstrating an improvement in survival with dacarbazine relative to BSC / any other control agent.[12;13]

4.2.2 RCTs excluded from further discussion

Not applicable

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1 Key aspects of listed RCTs

KEYNOTE-006:[23] Note: Follow-up in this study is ongoing, prior to final analysis being conducted)

Trial design:

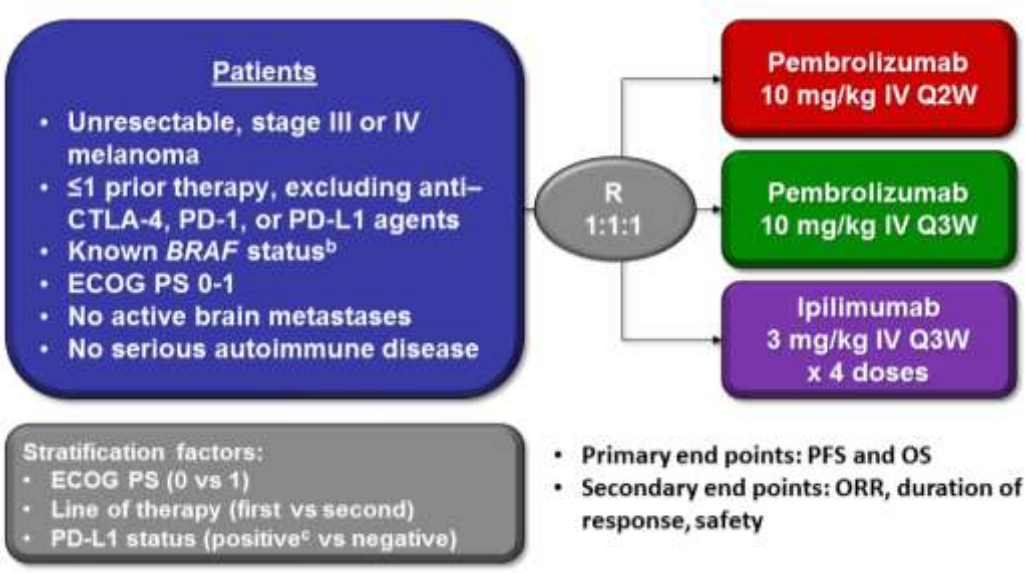
KEYNOTE-006 was a randomised, controlled, open-label, three-arm, phase III pivotal study of two dosing regimens of intravenous (IV) pembrolizumab versus ipilimumab in patients with unresectable or metastatic melanoma who had not received ipilimumab treatment (i.e. naïve to treatment with ipilimumab).

Patients randomised to one of the pembrolizumab arms received up to 24 months of pembrolizumab as IV infusion at a dose of 10 mg/kg Q2W or Q3W, until disease progression, intolerable toxicity, confirmed complete response, withdrawal of consent, or they required another form of antineoplastic therapy as determined by the Investigator.

Patients randomised to the ipilimumab arm received ipilimumab at 3 mg/kg as IV infusion Q3W for a total of 4 doses.

The design of KEYNOTE-006 is depicted in Figure 5 below

Figure 5: KEYNOTE-006 - Study design



Source: Ribas et al (2015)[1]
R= Randomised
[b] Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumour-related symptoms or evidence of rapidly progressing disease.
[c] Defined as membranous PD-L1 expression in ≥1% of tumour cells as assessed by IHC using the 22C3 antibody

In order to best evaluate the overall survival objective of this study, patients who progressed during the study were not allowed to cross-over from one arm to the other as part of study therapy.

In the treatment and evaluation phase, the study was designed to closely monitor patients with safety follow-up and disease assessments for 2 years in the absence of disease progression or other study discontinuation criteria. After the baseline tumour evaluation, tumour assessment during the study was performed by radiological scans. Disease assessments on all arms of the study occurred on the following schedule:

- First scheduled disease assessment: week 12
- Disease assessments every 6 weeks from week 18-48
- Disease assessments every 12 weeks from week 48-96

Patients were evaluated for tumour response and patient management by sites based on the Immune Related Response Criteria (irRC)[77] by the investigator with site radiology reading. Copies of tumour images were collected and provided to a central imaging vendor, and subjected to independent central review, which utilised RECIST 1.1 criteria[78] for response assessment.

Patients in complete response (CR), partial response (PR), or stable disease (SD) at the week 96 visit and who have completed 2 years of treatment/evaluations were to go into the post-treatment follow-up phase of the study.

Patients who had a confirmed CR by two scans ≥4 weeks apart and who had been on pembrolizumab treatment for at least 6 months were allowed to discontinue pembrolizumab treatment at the discretion of the investigator after receiving at least two doses beyond the initial determination of CR. Patients who stopped study treatment in CR were to continue undergoing disease evaluations with imaging studies as otherwise scheduled in the protocol, and in the event of disease recurrence, treatment with pembrolizumab was permitted to be resumed in these patients (i.e. second-course treatment).

If receiving pembrolizumab as second-course treatment, patients were to follow the same schedule of pembrolizumab treatment to which they were initially allocated and were to be followed with study visits and disease assessments as if they were starting study therapy anew (i.e. first scheduled disease assessment at week 12 and then every 6 weeks until week 48). Second Course treatment with pembrolizumab could be given for up to 12 additional months. Patients were eligible for second-course treatment only one time. Patients who discontinued study therapy in the second-course treatment phase for any reason

(progression of disease, AEs, or any other reason) were to have a post-study visit within 30 days and then undergo survival follow-up. The full eligibility criteria for second-course treatment with pembrolizumab are provided in Appendix 4.

Patients randomised to the ipilimumab arm were to be followed for safety and disease status until disease progression, intolerable toxicity, or withdrawal of the consent. Patients who stopped ipilimumab with SD or better and subsequently progressed were not allowed to be retreated with ipilimumab as part of planned study therapy. In the event that an investigator wished to re-treat a patient with ipilimumab, it was necessary for the patient to be discontinued from the study, but the patient was still to undergo survival follow-up.

Although KEYNOTE-006 was conducted as an open-label study, in order to ensure data integrity, the analysis and reporting team were blinded to the treatment assignments. Additionally, the independent radiologist(s) performed the central imaging review without knowledge of treatment assignments.

During the course of this study, the Data Monitoring committee (DMC) monitored all safety information to ensure patient safety in accordance with a separate charter. The DMC were also responsible for evaluating the data at the planned interim analyses and making recommendations of stopping or continuing the study according to a separate charter. Depending on the recommendation of the DMC, the study sponsor was permitted to prepare a regulatory submission after an interim analysis. In this scenario, the analysis and reporting team would be unblinded to treatment assignments, and remain unblinded for the remainder of the study.

Eligibility criteria:

Key inclusion criteria:

A patient must have met all of the following criteria to be eligible to participate in this study:

1) Histologically-confirmed diagnosis of unresectable Stage III or metastatic melanoma not amenable to local therapy (excluding uveal or ocular melanoma)
2) At least one measurable lesion
3) No prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (first line) or one prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (second line)

4) Patients must have testing for a BRAF mutation prior to study entry. Patients with $BRAF^{V600}$ mutant melanoma may have received prior BRAF inhibitor therapy as first-line systemic therapy and be eligible for this study as second line treatment. At the discretion of the investigator, patients with $BRAF^{V600}$ mutant melanoma who have NOT received a BRAF inhibitor were also eligible for this study as first line treatment if they met the following additional criteria:
    - Lactose dehydrogenase (LDH) < local upper limit of normal (ULN)
    - No clinically significant tumor related symptoms in the judgment of the investigator
    - Absence of rapidly progressing metastatic melanoma in the judgment of the investigator
5) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
6) Archived tissue sample or new biopsy sample
7) Female participants of childbearing potential and male participants must agree to use effective contraception from Visit 1 to 120 days after the last dose of study drug; male participants must agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study drug

Key exclusion criteria:

Patients who met any of the following criteria were not eligible to participate in this study:

1. Prior treatment with ipilimumab or other anti-cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) agent or any anti-programmed cell death (PD-1 or PD-L2) agent
2. Chemotherapy, radioactive, or biological cancer therapy within four weeks prior to the first dose of study drug, or not recovered from adverse events caused by cancer therapeutics administered more than four weeks earlier
3. Currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of the first dose of study drug (a patient in the Survival follow-up phase of an investigational agent where no further treatment is expected is eligible)
4. Expected to require any other form of systemic or localised antineoplastic therapy while on study
5. On any systemic steroid therapy within one week before the planned date for first dose of randomised treatment or on any other form of immunosuppressive medication
6. History of a malignancy (other than the disease under treatment in the study) within 5 years prior to first study drug administration, excluding adequately treated Stage 1 or Stage 2 basal/squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other in situ cancers.

7. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis; participants with previously treated brain metastases are eligible
8. Severe hypersensitivity reaction to treatment with another monoclonal antibody (mAb)
9. Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents
10. Active infection requiring systemic therapy
11. Known history of Human Immunodeficiency Virus (HIV)
12. Known history of or positive for Hepatitis B or C
13. Known psychiatric or substance abuse disorder
14. Regular user (including recreational use) of illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol)
15. Pregnant or breastfeeding, or expecting to conceive, or father children within the projected duration of the study

Settings and locations where the data were collected:

KEYNOTE-006 is a global study in which patients were enrolled across 83 sites in the following 16 countries:

Australia, Austria, Belgium, Canada, Chile, Colombia, France, Germany, Israel, Netherlands, New Zealand, Norway, Spain, Sweden, UK, USA.

The study was run in specialist oncology departments. Patients received treatment as day care patients.

Trial drugs and concomitant medications:

Patients were randomised to receive pembrolizumab 10 mg/kg Q2W (n=279), pembrolizumab 10 mg/kg Q3W (n=277) or ipilimumab 3 mg/kg Q3W (n=278) in a 1:1:1 ratio, stratified by line of prior therapy, PD-L1 expression status, and ECOG performance status.

Pembrolizumab was administered as an IV infusion for a total of 24 months or, until disease progression, intolerable toxicity, confirmed complete response, or withdrawal of the consent. Ipilimumab was administered as an IV infusion for a total of 4 doses.

Primary, secondary and tertiary outcomes

Primary objectives:

The co-primary endpoints of KEYNOTE-006 were:

- Progression-free survival (PFS), defined as the time from randomisation to the first documented disease progression (based on blinded independent central review using RECIST 1.1[78]) or death due to any causes, whichever occurs first
- Overall survival (OS), defined as the time from randomisation to death due to any cause.

The study is considered to have met its study objective if at least one pembrolizumab arm is superior to ipilimumab in PFS at an interim analysis or at least one pembrolizumab arm is superior to ipilimumab in OS at either an interim analysis or the final analysis of OS.

Secondary objectives:

The secondary objectives of the study were as follows:

- To evaluate safety, tolerability and adverse experience (AE) profile of pembrolizumab versus ipilimumab.
- To evaluate overall response rate (ORR) in patients with advanced melanoma receiving either pembrolizumab or ipilimumab.
- To evaluate OS, PFS and ORR in a subgroup of patients with high PD-L1 expression level receiving either pembrolizumab or ipilimumab.
- To further characterize the pharmacokinetics of pembrolizumab

ORR was defined as the proportion of the patients in the analysis population who have best response as CR or PR. Responses were based on blinded independent central review using RECIST 1.1.[78]

Exploratory objectives:

The exploratory objectives were as follows:

- To evaluate response duration in patients with advanced melanoma receiving either pembrolizumab or ipilimumab
- To evaluate health-related quality of life (HRQoL) changes from baseline in patients with advanced melanoma receiving either pembrolizumab or ipilimumab using the eEORTC-QLQC30.

- To evaluate health utility changes from baseline in patients with advanced melanoma receiving either pembrolizumab or ipilimumab using the EQ-5D.
- To evaluate PFS and ORR based on irRC,[77] in patients with ipilimumab naive melanoma treated with pembrolizumab.

Populations used for analysis:

The study population used for analysis of each endpoint is defined in section 4.4.2.

KEYNOTE-001 – Part D:[70]

Trial design:

KEYNOTE-001, which formed the basis of the regulatory submission for pembrolizumab (since supplemented with data from KEYNOTE-002[79] and KEYNOTE-006[23]) was a Phase I multi-centre, open-label study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and anti-tumour activity of pembrolizumab in patients with locally advanced or metastatic melanoma (ipilimumab-naïve or previously treated with ipilimumab), NSCLC, or carcinoma.

Although KEYNOTE-001 is labelled a Phase I study due to its initial dose escalation component, it evolved into multiple Phase II-like sub-studies in melanoma and NSCLC through a series of expansion cohorts in these types of cancer. The trial was initially designed as a standard dose escalation trial, and was the first in human study of pembrolizumab. This comprised Part A of KEYNOTE-001. During this part of the study, patients with melanoma were enrolled and had an objective response to treatment, so the study was expanded to evaluate efficacy in melanoma in Part B (now Part B1). Through a series of amendments, KEYNOTE-001 evolved into 4 Phase II-like melanoma sub-studies, known as Parts B1, B2, B3, and D. In addition, KEYNOTE-001 was further expanded in Parts C and F to evaluate the activity of pembrolizumab in NSCLC. Further details on Part B1, B2 and B3 and D are provided in Table 9 below

Table 9: KEYNOTE-001 – Summary of Parts B1, B2, B3 and D

B1: Advanced melanoma patients: Ipilimumab-naïve and ipilimumab-treated. Non randomised cohort	57 patients at 10 mg/kg 2QW, 56 patients at 10 mg/kg Q3W 22 patients at 2 mg/kg Q3W
B2: Advanced melanoma patients: Ipilimumab-refractory. Randomised to two doses	89 patients at 2 mg/kg Q3W 84 patients at 10 mg/kg Q3W

B3: Mixed population: Advanced melanoma patients: Ipilimumab-naïve and ipilimumab-treated. Randomised to two dosing schedules	125 patients at 10 mg/kg Q3W 123 patients at 10 mg/kg Q2W
D (population of relevance to decision problem) **Advanced melanoma patients:** **Ipilimumab-naïve only.** **Randomised to two doses**	**51 patients at 2 mg/kg Q3W** **52 patients at 10 mg/kg Q3W**

Part D was a randomised expansion cohort of KEYNOTE-001, comprised of 103 patients naïve to treatment with ipilimumab who are allowed up to 2 prior systemic treatment regimens. In addition to evaluating the tolerability and safety of each dose of pembrolizumab in this population, Part D was also designed to further evaluate the preliminary evaluation of anti-tumour activity in melanoma. Part D comprises the key patient population from KEYNOTE-001 supporting the use of pembrolizumab in a patient population comparable to that covered by the KEYNOTE-006 trial.

The 103 patients naïve to treatment with ipilimumab who were included in Part D were randomised to receive one of the following regimens:

- Pembrolizumab 2mg/kg Q3W (n=51)
- Pembrolizumab 10 mg/kg Q3W (n=52)

Study treatment continued until disease progression, unacceptable toxicity, or the investigator considered it in the best interest of a patient to discontinue study therapy.

KEYNOTE-001 was conducted as an open-label study (i.e., patients, investigators, and study sponsor personnel were aware of patient treatment assignments after each patient was enrolled and treatment assigned). However, for those randomised cohorts, such as Part D, treatment assignment was based on a computer-generated allocation schedule generated in-house to maintain randomness.

Radiographic Assessment

For all patients, it was required that baseline tumour imaging (CT or MRI, with a preference for CT) examinations must be performed within 30 days before enrolment. The same imaging technique as used at baseline had to be used throughout the study.

Part D: Following radiological tumour assessment at screening, patients enrolled in Part D had their first radiological assessment of tumour response status at Week 12 (± 1 week) unless clinical indication warranted earlier imaging. If disease assessment at Week 12

showed stable disease (SD), treatment was to continue and the next imaging was performed at approximately Week 24. If disease assessment at Week 12 showed a complete response (CR) or partial response (PR), imaging was repeated at Week 16 to confirm response, per irRC recommendations.[77] Subsequent imaging was performed at Week 24 and every 12 weeks subsequently.

If imaging at 12 weeks showed progressed disease (PD), the investigator had the discretion to either keep a patient on study treatment or stop study treatment until repeat imaging was repeated approximately 4-6 weeks later, to confirm PD. Patients deemed clinically unstable were not required to have repeat imaging for confirmation. If repeat imaging showed an objective response or stable disease, treatment with pembrolizumab continued/resumed and the next imaging studies were conducted approximately at Week 24, and every 12 weeks subsequently. If repeat imaging at Week 16 confirmed PD, patients were discontinued from study therapy.

Eligibility criteria:

Key inclusion criteria for Part D of KEYNOTE-001:

1. Histological or cytological diagnosis of melanoma with progressive locally advanced or metastatic disease that was not amenable to definitive local therapy with curative intent. Part D of KEYNOTE-001 enrolled patients who were naive to treatment with ipilimumab and had not received more than 2 prior systemic treatment regimens for treatment of melanoma.
2. Measurable disease as defined per irRC.[77]
3. ECOG performance status[80] of 0 or 1.
4. Adequate organ function as defined in study protocol.

Key exclusion criteria (Part D of KEYNOTE-001):

1) Chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study therapy, or who had not recovered to CTCAE grade 1 or better from the adverse events due to cancer therapeutics administered more than 4 weeks earlier.
2) Participation in a study of an investigational agent or using an investigational device within 30 days of administration of pembrolizumab (this does not include participation in the follow-up phase of a study).
3) Expected to require any other form of antineoplastic therapy while on study.

4) Medical condition requiring chronic systemic steroid therapy or on any other form of immunosuppressive medication (however patients using physiologic replacement doses of hydrocortisone, or its equivalent, will be considered eligible for this study).
5) Risk factors for bowel obstruction or bowel perforation (including but not limited to a history of acute diverticulitis, intra-abdominal abscess, abdominal carcinomatosis).
6) Known history of a hematologic malignancy, malignant primary brain tumour or malignant sarcoma, or of another malignant primary solid tumour, unless the patient had undergone potentially curative therapy with no evidence of that disease for 5 years.
7) Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
8) Previous history of severe hypersensitivity reaction to treatment with any mAb.
9) History of non-infectious pneumonitis that has required a course of oral or intravenous steroids to assist with recovery, or interstitial lung disease.
10) Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents (patients with hypothyroidism not from autoimmune disease that is stable on hormone replacement will not be excluded from the study).
11) Received prior treatment targeting PD-1: PD-L1 axis or CTLA, or was previously randomised in any pembrolizumab trial.

Settings and locations where the data were collected:

The KEYNOTE-001 study was conducted in the following countries:

Australia, Canada, Denmark, France, Germany, Israel, Italy, Norway, South Korea, Spain, Taiwan, UK, USA.

The study was run in specialist oncology departments. Patients received treatment as day care patients.

Trial drugs and concomitant medications:

A total of 103 patients were included in Part D of KEYNOTE-001. Patients were randomised to each of the following study arms:

- Pembrolizumab 2 mg/kg dose Q3W (n = 51)
- Pembrolizumab 10 mg/kg dose Q3W (n = 52)

Primary, secondary and tertiary outcomes

Primary efficacy endpoint:

Response rate (RR) served as the primary efficacy endpoint to demonstrate the anti-tumour activity of pembrolizumab in the population enrolled under Part D of KEYNOTE-001. The primary measure for assessment of tumour response was based on RECIST 1.1 [78] by blinded central reviewers and the secondary measure was based on irRC [77] as assessed by investigators.

Secondary efficacy endpoint:

Disease Control Rate (DCR), response duration and PFS based on both RECIST 1.1,[78] and irRC[77] and OS served as secondary endpoints in this study.

Populations used for analysis:

The study population used for analysis of each endpoint is defined in section 4.4.2.

4.3.2 Comparative summary of the methodology of the RCTs

Table 10: Comparative summary of trial methodology

Trial number (acronym)	KEYNOTE-006	KEYNOTE-001 (Part D)
Location	Global study conducted in the following 16 countries: Australia, Austria, Belgium, Canada, Chile, Colombia, France, Germany, Israel, Netherlands, New Zealand, Norway, Spain, Sweden, UK, USA.	The full KEYNOTE- 001 study was conducted across the following countries: Australia, Canada, Denmark, France, Germany, Israel, Italy, Norway, South Korea, Spain, Taiwan, UK, USA
Trial design	Phase III randomised, controlled, open-label, three-arm, pivotal study of two dosing regimens of intravenous (IV) pembrolizumab versus ipilimumab in patients with unresectable or metastatic melanoma previously untreated with ipilimumab (i.e. naïve to treatment with ipilimumab).	Phase I open-label study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and anti-tumour activity of pembrolizumab in patients with locally advanced or metastatic melanoma (ipilimumab-naïve or previously treated with or refractory to ipilimumab), NSCLC, or carcinoma. Initially designed as a standard dose escalation trial (now Part A), the study was expanded to evaluate efficacy in melanoma in Part B (now Part B1). Through a series of amendments, KEYNOTE-001 evolved into 4 Phase II-like melanoma sub-studies, known as Parts B1, B2, B3, and D. In addition,

		KEYNOTE-001 was further expanded in Parts C and F to evaluate the activity of pembrolizumab in NSCLC. Part D represents the population of relevance to this submission
Key eligibility criteria for participants	• Histologically-confirmed diagnosis of unresectable Stage III or metastatic melanoma not amenable to local therapy (excluding uveal or ocular melanoma). • At least one measurable lesion. • No prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (first line) or one prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (second line). • No prior treatment with ipilimumab or other anti-cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) agent or any anti-programmed cell death (PD-1 or PD-L2) agent. • Patients must have testing for a BRAF mutation prior to study entry. Patients with $BRAF^{V600}$ mutant melanoma may have received prior BRAF inhibitor therapy as first-line systemic therapy. • ECOG performance status of 0 or 1. • Archived tissue sample or new biopsy sample.	**Part D:** • Histological or cytological diagnosis of melanoma with progressive locally advanced or metastatic disease that was not amenable to definitive local therapy with curative intent. Part D of KEYNOTE-001 enrolled patients who were naive to treatment with ipilimumab and had not received more than 2 prior systemic treatment regimens for treatment of melanoma. • Measurable disease as defined per irRC. • ECOG performance status of 0 or 1. • Adequate organ function as defined in study protocol.
Settings and locations where the data were collected	The study was run in specialist oncology departments. Patients received treatment as day care patients	The study was run in specialist oncology departments. Patients received treatment as day care patients
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=) and comparator(s) (n=)** **Permitted and disallowed concomitant medication**	Patients were randomised in a 1:1:1 ratio, stratified by line of prior therapy, PD-L1 expression status, and ECOG performance status to receive one of the following: • pembrolizumab 10 mg/kg Q2W (n=279) • pembrolizumab 10 mg/kg Q3W (n=277) • ipilimumab 3mg/kg Q3W (n=278) <u>Acceptable concomitant medicines</u> • All treatments considered by the investigator to be necessary for a patient's welfare. <u>Disallowed concomitant medicines:</u> • Antineoplastic systemic	A total of 103 patients were included in Part D of KEYNOTE-001. Patients were randomised to each of the following study arms: • pembrolizumab 2 mg/kg dose Q3W (n= 51) • pembrolizumab 10 mg/kg dose Q3W (n = 52) <u>Acceptable concomitant medicines</u> • All treatments considered by the investigator to be necessary for a patient's welfare. <u>Disallowed concomitant medicines:</u>

	chemotherapy or biological therapy • Immunotherapy including corticosteroids, except for treatment of potential immune-related AEs during the study • Investigational agents other than pembrolizumab • Radiation therapy (note: radiation therapy to a symptomatic solitary lesion may be allowed after consultation with the study sponsor). • Live vaccines within 30 days prior to the first dose of study therapy and while participating in study.	• Any other investigational agent • Any other form of antineoplastic therapy • chronic systemic steroid therapy or on any other form of immunosuppressive medication • chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study therapy • Live vaccines within 30 days prior to the first dose of study therapy and while participating in study.
Primary outcomes (including scoring methods and timings of assessments)	The co-primary objectives of this study were as follows: • PFS: defined as the time from randomisation to the first documented disease progression or death due to any cause, whichever occurs first • OS: defined as the time from randomisation to death due to any cause Primary analysis of PFS was based on blinded independent central review using RECIST 1.1 criteria. ITT population served as the primary population for the analyses of PFS and OS. First radiologic assessment of tumour response occurred at Week 12 following first dose of study medication. Scans were obtained every 6 weeks until Week 48, and every 12 weeks until week 96.	Primary efficacy endpoint: • RR to demonstrate the anti-tumour activity of pembrolizumab in the population enrolled under Part D of KEYNOTE-001 Primary measure for assessment of tumour response was based on RECIST 1.1 by blinded central reviewers and secondary measure was based on irRC as assessed by investigators. Primary efficacy analyses were based on the FAS population. First radiological disease assessment on study occurred at Week 12 (± 1 week) unless clinical indication warranted earlier imaging.
Secondary/ tertiary outcomes (including scoring methods and timings of assessments)	The secondary objectives were as follows: • ORR • OS, PFS, and ORR in the subgroup of patients with high PD-L1 expression level • Safety, tolerability and AE profile of pembrolizumab versus ipilimumab Primary analysis of ORR was based on blinded independent central review using RECIST 1.1 criteria (ITT population) The exploratory objectives were as follows: • Response duration • HRQoL changes from baseline using the EORTC-QLQC30. • Patient utilities using the EuroQoL	Secondary efficacy endpoints: • DCR • Response duration • PFS based on both irRC and RECIST 1.1 • OS Analyses of PFS and OS were based on the APaT population.

	EQ-5D. • PFS and ORR based on irRC HRQoL questionnaires were performed at baseline through week 36 as well as the end of treatment, and 30-day safety follow-up visit.	
Pre-planned subgroups	Subgroup analysis will be conducted by line of therapy, PD-L1 expression status and ECOG performance status. Additionally, patients with high PD-L1 expression level are of special interest in this study.	Not Applicable.

APaT= All Patients as Treated; DCR = Disease Control Rate; FAS = full analysis set; ITT = intention to treat; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RR = response rate

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

4.4.1 Statistical analysis

KEYNOTE-006[23]

Primary hypothesis

The study hypotheses were as follows:

- *Pembrolizumab is superior to ipilimumab in PFS.*
- *Pembrolizumab is superior to ipilimumab in OS.*

Interim analysis and stopping guidelines

KEYNOTE-006 had two planned interim efficacy analyses. The primary objective for the first interim analysis (IA1) was to perform the primary analysis of PFS. The primary objective of the second interim analysis (IA2) was to evaluate treatment effect based on OS.

OS superiority was to be tested using the Hochberg step-up procedure. Using this procedure, if the p-value for both pembrolizumab arms is <0.5%, both pembrolizumab arms are superior to the ipilimumab arm in OS; if the least significant (larger) p-value is >0.5% then the most significant (smaller) p-value needs to be compared with 0.25% (0.5%/2). With 200 OS events between each pembrolizumab arm and ipilimumab arm, a p-value of 0.5% corresponds to an empirical hazard ratio (HR) of 0.6947, (i.e., approximately >4.8 months of improvement when median OS is 11 months in ipilimumab arm); a p-value of 0.25% corresponds to an empirical HR of 0.6724 (i.e., approximately >5.4 months of improvement when median OS is 11 month in the ipilimumab arm).

An analysis of long-term PFS effect was also to be carried out at IA2. Approximately 440-485 PFS would have been observed across three arms. Each pembrolizumab arm will be compared to the ipilimumab arm on PFS at one-sided alpha of 0.05%. An observed HR for PFS of approximately ≤ 0.6839 corresponds to superiority in PFS at $\alpha = 0.05\%$ (one-sided) based on 300 PFS events between a pembrolizumab arm and ipilimumab arm. This HR corresponds to a median PFS of 4.4 months for pembrolizumab versus 3 months for ipilimumab.

Table 11 summarizes the pre-specified timing, sample size and decision guidance at each interim analysis. Accrual was to continue during the interim analyses. The protocol specified that the final analysis will take place when approximately 435 deaths have occurred across three arms, or all patients have been followed up for 21 months, whichever occurs first.

Table 11: KEYNOTE-006: Summary of timing, sample size and decision guidance at each interim analysis

	Interim analysis 1 (primary analysis of PFS)	**Interim analysis 2**
Endpoints	PFS and OS	PFS and OS
Approximate timing	All patients have been followed up for 6 months and approximately 260 PFS events have been observed across three arms	When minimum follow-up is at least 9 months and approximately 290 deaths have been observed unless it takes longer than 12 months of follow-up to observe 290 deaths in which case, the analysis will be performed when minimum follow-up is 12 months.
Sample size the primary analysis is based upon	Approximately 260 PFS events and approximately 235 deaths across three arms	approximately 440-485 PFS events, approximately 290 deaths across three arms
Stop early for futility[1]	PFS doesn't meet the efficacy bar below AND the OS improvement is < 1 month (empirical OS HR>0.9167[3]) for both pembrolizumab arms	Not Applicable
Stop early for efficacy	(one-sided) p-value for OS <0.002% for both pembrolizumab arms or p-value <0.001% for one pembrolizumab arm (corresponds to empirical HR <0.5223 or 0.5095, median OS improvement >10.1 or 10.6 months respectively[3,4])	(one-sided) p-value <0.5% for both pembrolizumab arms or p-value <0.25% for one pembrolizumab arm (corresponds to empirical HR <0.6947 or 0.6724, median OS improvement >4.8 or 5.2 months respectively[3,4])
Efficacy bar at IA1 (primary analysis of PFS)	(one-sided) p-value for PFS <0.2% for at least one pembrolizumab arm (corresponds to empirical HR 0.6511, median PFS improvement >1.6 months[2])	Not Applicable

[1] Totality of data will be reviewed to determine whether the study will be terminated or halted (details to be provided in DMC charter).
[2] Assume median PFS in the control arm is 3 months. Estimates of empirical effect in brackets are approximates.
[3] Assume median survival time in the control arm is 11 months. Estimates of empirical effect in brackets are approximates.
[4] Hochberg step-up procedure will be used for OS testing at both the second interim analysis and the final analysis, giving equal weight to the two pembrolizumab arms, if neither is discontinued prior to the analyses.

Sample size

834 patients were randomised with a 1:1:1 ratio, (stratified by line of therapy [first vs. second], PD-L1 expression [high vs. low expression], and ECOG performance status [0 vs. 1]) into the two pembrolizumab arms (10 mg/kg Q2W and 10 mg/kg Q3W) and the ipilimumab arm. The study originally planned to enrol approximately 645 eligible patients, but the protocol acknowledged that as the study was event driven and the sample size calculation is driven by survival events, the number of patients and follow-up time were subject to change.

The sample size for each line of therapy was capped at 60% of the total patients. The sample size calculation was based on the following assumptions:

1) OS follows an exponential distribution with a median of 10-11 months in the control arm;
2) The HR for OS between pembrolizumab and control is 0.70 (deemed to be clinically meaningful in this population);
3) An enrolment period of 6 months and a minimum of 21 months follow-up after enrolment completion; and
4) A yearly drop-out rate of 2%.

The overall type I error rate for KEYNOTE-006 was strictly controlled at 2.5% (one-sided) with 0.5% allocated to PFS and 2.0% allocated to the overall OS hypothesis. The study protocol specified that primary analysis of PFS will to be carried out at IA1 at 0.4% alpha-level (one-sided). An analysis of long-term PFS effect was to be carried out at IA2 at 0.1% alpha-level (one-sided). The Bonferroni method will be used for multiplicity adjustment of the two pembrolizumab arms at each interim analysis with each pembrolizumab arm tested at 0.2% (one-sided) at IA1, and 0.05% (one-sided) at IA2. ORR will be tested sequentially at IA1 if the primary objective in PFS is met. If any of the two pembrolizumab arms is demonstrated to have a superior PFS and ORR to ipilimaumb at IA1, or a superior PFS to ipilimumab at the IA2, the corresponding alpha level will be rolled into the overall OS hypothesis (i.e. the overall OS hypothesis will be tested at ≥2.0%), and the ORR will be tested at the corresponding alpha level sequentially if the OS hypothesis is rejected..

At the final analysis, alpha for OS is between 1.5% and 2% and the actual alpha depends on how many pembrolizumab arms have a superior PFS and ORR compared to ipilimumab at IA1 and how many pembrolizumab arms have a superior PFS at IA2. See Table 12 for alpha for OS at final analysis under different scenarios. The Hochberg step-up procedure will be

used for OS testing at each interim analysis and the final analysis, giving equal weight to the two pembrolizumab arms, if neither is discontinued prior to the analyses.

Table 12: KEYNOTE-006 - Alpha for OS under different scenarios

Number of pembrolizumab arms demonstrating superior PFS and ORR at IA1	0	0	0	1	1	1	2	2	2
Number of pembrolizumab arms demonstrating superior PFS at IA2	0	1	2	0	1	2	0	1	2
One-sided alpha for OS at IA2	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
One-sided alpha for OS at final analysis	1.5%	1.55%	1.6%	1.7%	1.75%	1.8%	1.9%	1.95%	2.0%
One-sided alpha for OS overall	2.0%	2.05%	2.1%	2.2%	2.25%	2.3%	2.4%	2.45%	2.5%

With multiplicity strategy described above, the overall type I error rate will be controlled at the 2.5% level (one-sided).

The first planned interim analysis was due to occur when all patients had been followed up for 6 months and approximately 260 PFS events had been observed across the two pembrolizumab arms and the ipilimumab arm. At that time, approximately 180 PFS events were expected to have occurred between a pembrolizumab arm and the ipilimumab arm. With 180 PFS events, the study has at least 95% power to detect a true HR of 0.5 (100% improvement in PFS) at $\alpha = 0.2\%$, one-sided.

With at least 2% of alpha allocated to OS, the reference type I error rate is at least 1% between one pembrolizumab arm and control arm. With 300 OS events between a pembrolizumab arm and the ipilimumab arm, the study has 85% power to demonstrate superiority when the true HR for OS is 0.70 at type I error rate of 2.0% (one-sided).

The study is considered to have met its study objective if at least one pembrolizumab arm is superior to ipilimumab in PFS at an interim analysis OR at least one pembrolizumab arm is superior to ipilimumab in OS at either an interim analysis or the final analysis of OS.

Statistical methods used to compare groups for primary and secondary outcomes

The statistical methods for efficacy analysis of the primary and secondary efficacy endpoints were as follows (summarised in Table 13 below):

PFS

The same stratification factors used for randomisation were applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the patients who have PD, the true date of disease progression was to be approximated by the date of first assessment at which PD is objectively documented using RECIST 1.1 criteria,[78] regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Patients without documented PD/death were censored at the last disease assessment date.

OS

The same stratification factors used for randomisation were applied to both the stratified log-rank test and the stratified Cox model. The Kaplan-Meier (KM) estimates of OS rate at 12 months were to be compared between each of the pembrolizumab arms and the ipilimumab arm and proportionality of HR over time were to be explored.

Since patients in the ipilimumab arm were expected to discontinue treatment earlier compared to patients in the pembrolizumab arms, and patients who discontinued ipilimumab were likely to receive other PD-1 treatments similar to pembrolizumab after discontinuation, the protocol pre-specified that the Rank Preserving Structural Failure Time (RPSFT) model will be used to control for receipt of non-study treatment. The 95% confidence intervals for the HR for OS before and after proper adjustment of the cross-over effect (if any) will be provided at the final analysis (therefore not of relevance to IA1 and IA2 results, presented in section 4.7)

Table 13: KEYNOTE-006 - Primary analysis strategy for efficacy endpoints

Endpoint/variable (description, time point)	Statistical method	Analysis population
Primary		
PFS	Testing: Stratified Log-rank test used to assess treatment difference in PFS. Estimation: Stratified Cox proportional hazard model with Efron's method of tie handling used to assess magnitude of treatment difference between the treatment arm (HR and its 95% confidence interval (CI) reported). KM method for PFS curve estimation in each treatment group.	ITT
OS	Testing: Stratified Log-rank test used to assess treatment difference in survival. Estimation: Stratified Cox proportional hazard model with Efron's method of tie handling used to assess magnitude of treatment difference between the treatment arm (HR and its 95% confidence interval (CI) reported). KM method for OS curve estimation in each treatment group.	ITT
Secondary		
ORR	Stratified Miettinen and Nurminen method	FAS

[$] *Miettinen & Nurminen method; ITT = intention-to-treat; FAS = full analysis set*

Methods for additional analyses, such as subgroup analyses and adjusted analyses

The study protocol specified that the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint would be estimated and plotted within each category of the following classification variables:

- Age category (≤65 vs. >65 years)
- Sex (female, male)
- Race (white, non-white)
- ECOG status (0 vs. 1)
- Line of therapy (first vs second)
- Prior treatment with a BRAF or MEK inhibitor (yes vs. no)
- BRAF mutation status
- Region (US, Ex-US)
- PD-L1 expression (high vs. low) (depending on assay availability)
- Human leukocyte antigen (HLA-A*0201) (positive vs. negative) (depending on availability of data)
- Prior immunotherapy such as interferon, peg-interferon, and IL-2 (yes vs. no)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. Additionally, patients with high PD-L1 expression level are of special interest in this study.

KEYNOTE-001 (Part D)[70]

Primary hypothesis:

The study hypothesis was as follows:

Single agent pembrolizumab will show a clinically meaningful response rate (RR) in ipilimumab-naïve melanoma patients

Interim analysis and stopping guidelines

The study protocol specified that interim analyses of Part D ipilimumab-naive patients may be conducted as part of KEYNOTE-001 to assist with the dose-selection decision for planning phase 2 studies in melanoma patients.

Sample size

Part D of KEYNOTE-001 randomised 51 patients to pembrolizumab 2 mg/kg Q3W and 52 patients to pembrolizumab 10 mg/kg Q3W.

The study protocol had originally planned to randomise 88 ipilimumab-naive patients between each dose level, and stated the study has 80% power to detect 30% vs. 10%; or 90% power to detect 25% vs 5% in RR between the two dose levels at the 10% type I error rate (one-sided). A p-value of 10% approximately corresponds to a 12% empirical difference in RR.

Statistical methods used to compare groups for primary and secondary outcomes

A 95% confidence interval for RR was to be provided for each population and by dose/schedule as applicable. KM plots and descriptive statistics of PFS and OS, and descriptive statistics for analysis of response duration and tumour volumetric change were also to be provided.

Methods for additional analyses, such as subgroup analyses and adjusted analyses

In the assessment of anti-tumour activity in the melanoma population, patients in Part D were analysed by dose level.

4.4.2 Trial population included in primary analysis of the primary outcome and methods to take account of missing data

KEYNOTE-006[23]

Trial population

The intent-to-treat (ITT) population served as the primary population for the analysis of PFS, OS and ORR in this study. Patients were included in the treatment group to which they were randomised for the analysis using the ITT population. The primary analyses of PFS and ORR is based on blinded independent central review using RECIST 1.1.[78] Sensitivity analysis based on investigator's assessments using irRC[77] was also performed.

The All Patients as Treated (APaT) population was used for the analysis of safety data in this study. The APaT population consisted of all randomised patients who received at least one dose of study treatment. Patients were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population.

Missing data approach and censoring methods

Patients without documented death at the time of the final analysis were to be censored at the date of the last follow-up.

The approach for dealing with missing data in the KEYNOTE-006 population is described in Table 14 below:

Table 14: KEYNOTE-006: Approach for dealing with missing data

Endpoint/Variable Response (Description, time-point)	Missing Data Approach
Primary:	
PFS	Model based (censored at last assessment)
OS	Model based (censored at last date)
Secondary:	
ORR	Patients with missing data are considered non-responders

There were three sensitivity analyses planned, each with a different set of censoring rules and PD event definitions under various scenarios. The censoring rules for primary and sensitivity analyses are summarized in Table 15 below:

Table 15: KEYNOTE-006 - Censoring rules for primary and sensitivity analyses of PFS

Situation	Primary analysis†	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3*
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise	Censored at last disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment	Censored at last disease assessment before new anticancer treatment
PD or death documented after ≤1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥2 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death

† based on blinded independent central review using RECIST 1.1 criteria.
* based on investigator's assessment using irRC.

The study protocol specified that KM estimates of OS rate at 4 months and 6 months would be compared between each pembrolizumab arm and ipilimumab arm to explore the confounding effect of subsequent treatments. To further account for the possible

confounding effect, a sensitivity analysis of OS that censors patients at the time of initiation of new therapy would be performed and an OS analysis that treats initiation of new therapy as the time-dependent binary covariate would also be conducted.

KEYNOTE-001 (Part D)[70]

Trial population

The primary efficacy analyses were based on the Full Analysis Set (FAS) population. Patients with measurable disease at baseline (defined separately under investigator evaluation and central review), who received at least one dose of study treatment were included in the FAS population.

Analyses of PFS and OS are based on the APaT population that consists of all patients who received at least 1 dose of study treatment.

Missing data approach and censoring methods

Not Applicable

4.4.3 Statistical tests used in primary analysis

Table 16: KEYNOTE-006 - Summary of statistical analyses in the RCTs

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
KEYNOTE-006	• Pembrolizumab is superior to ipilimumab in PFS. • Pembrolizumab is superior to ipilimumab in OS.	The ITT population is the primary population for the analyses of PFS, OS and ORR. . The APaT population is used for the analysis of safety data in this study.	Survival event-driven study. Initially planned to randomise 645 patients with 1:1:1 ratio into two pembrolizumab arms (10 mg/kg Q2W and 10 mg/kg Q3W) and an ipilimumab 3 mg/kg Q3W arm (834 patients were finally randomised). Sample size calculation was based on the following assumptions: 1) OS follows an exponential distribution with a median of 10-11 months in the control arm, 2) HR for OS between pembrolizumab and control is 0.70, 3) an enrolment period of 6 months and a minimum of 21 months follow-up after enrolment completion, and 4) a yearly dropout rate of 2%. The overall type I error rate for was strictly controlled at 2.5% (one-sided) with 0.5% allocated to PFS and 2.0% allocated to the overall OS hypothesis.	Patients were permitted to withdraw at any time or be dropped from the study at the discretion of the investigator if any untoward effects occurred. Additionally, a patient could be withdrawn by the investigator or study sponsor if he/she violated the study plan or for administrative and/or other safety reasons. If a patient discontinued/withdrew prior to study completion, all applicable activities scheduled for the final study visit were to be performed at the time of discontinuation.

KEYNOTE-001 (Part D)	Single agent pembrolizumab will show a clinically meaningful response rate (RR) in ipilimumab-naïve melanoma patients.	The primary efficacy analyses were based on the FAS population. Analyses of PFS and OS were based on the APaT population.	Part D initially planned to randomise 88 ipilimumab-naive patients across the pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W study arms (51 patients were finally randomised to 2 mg/kg Q3W and 52 patients to 10 mg/kg Q3W). The study had 80% power to detect 30% vs. 10%; or 90% power to detect 25% vs 5% in RR between the two dose levels at the 10% type I error rate (one-sided). A p-value of 10% approximately corresponds to a 12% empirical difference in RR	Patients were permitted to withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a patient could be withdrawn by the investigator or the study sponsor if he/she violated the study plan or for administrative and/or other safety reasons. When a patient discontinued/withdrew prior to study completion, all applicable activities scheduled for the final study visit were performed at the time of discontinuation.

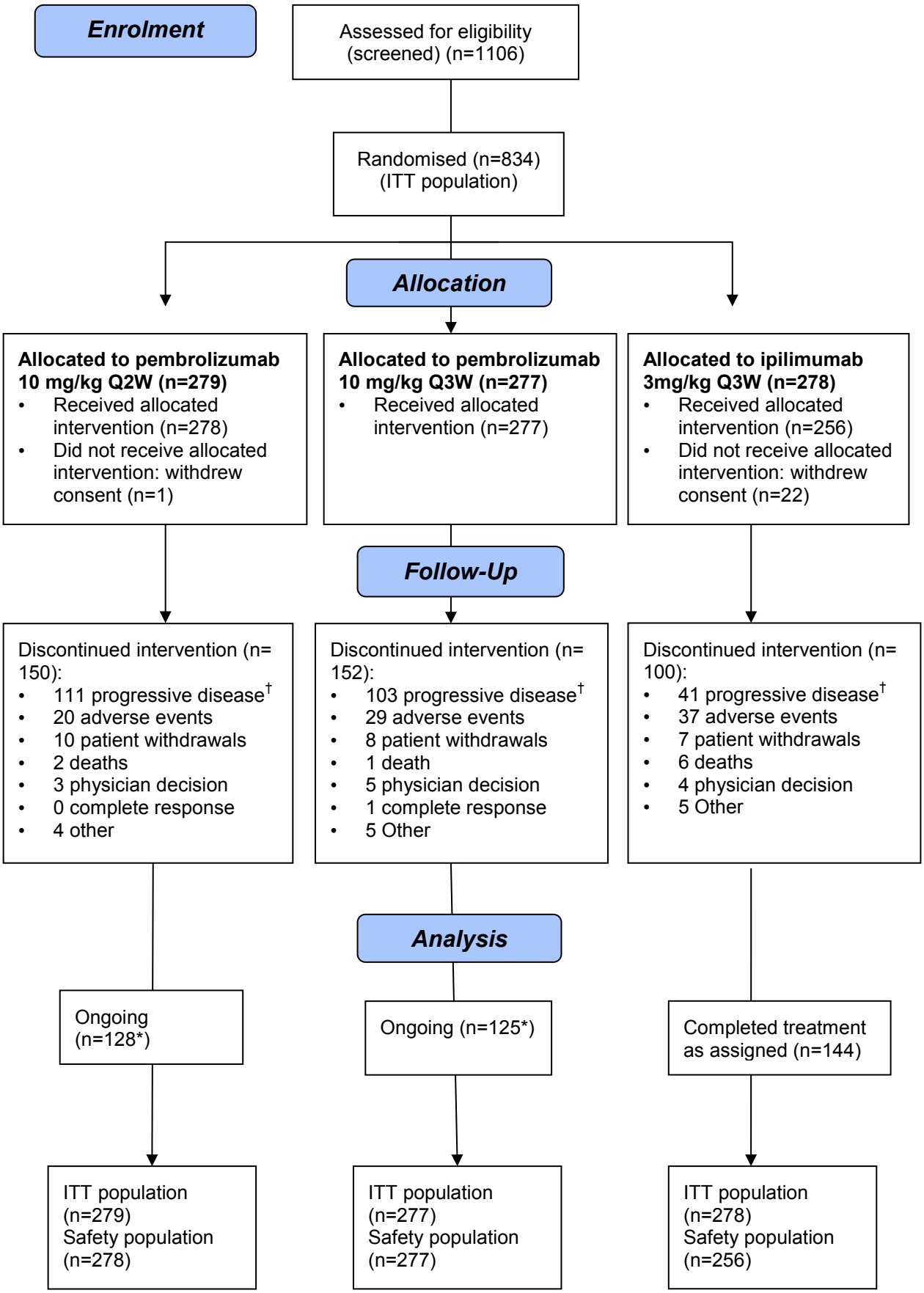
4.5 Participant flow in the relevant randomised controlled trials

4.5.1 Number of patients eligible to enter each trial, and crossover criteria

KEYNOTE-006

As KEYNOTE-006 is ongoing, the disposition of patients enrolled throughout the enrolment period (September 2013 – March 2014) is presented in Figure 6 below:

Figure 6: CONSORT diagram – KEYNOTE-006:

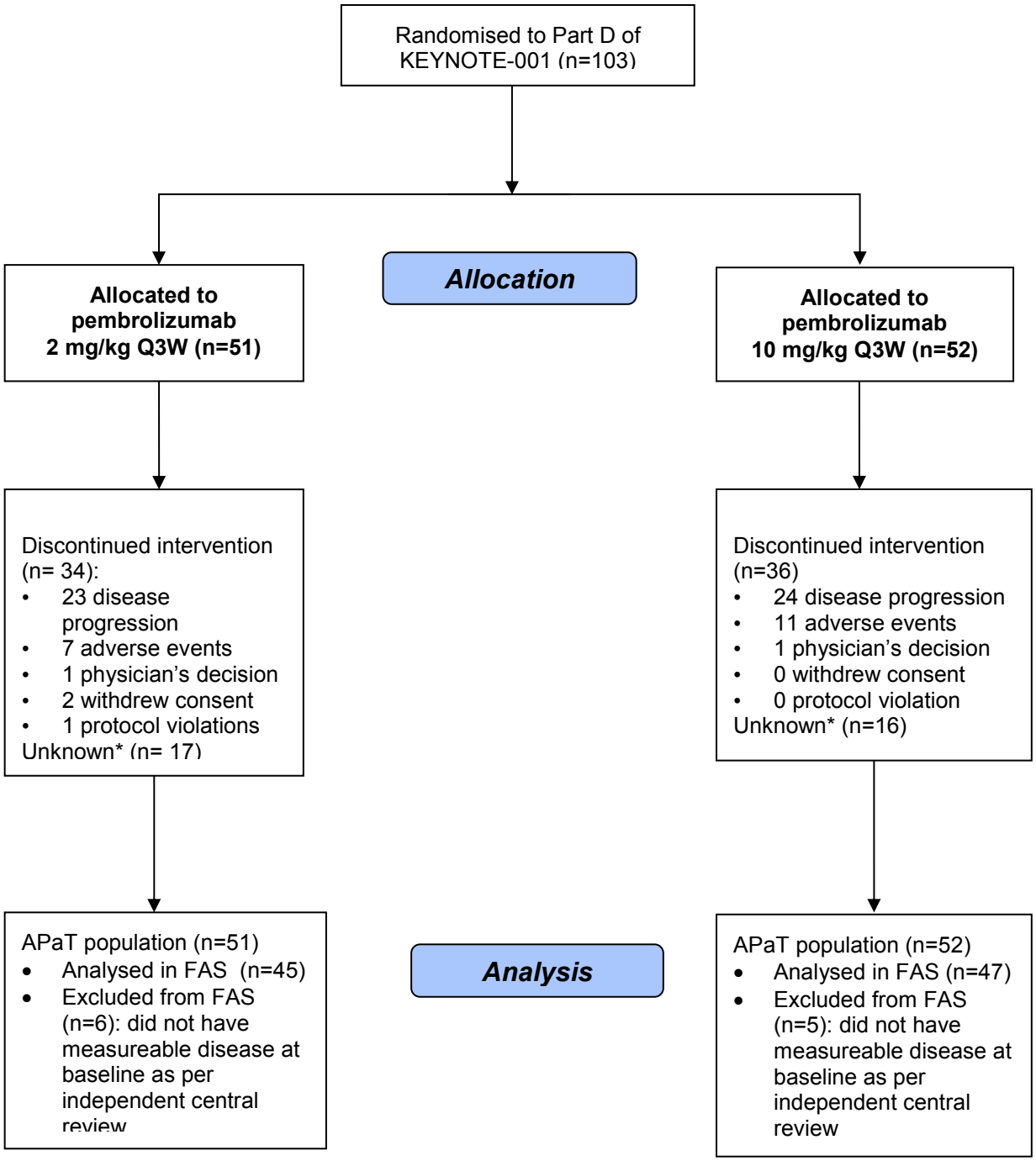


**Patients without a completed discontinuation form*
†Includes radiologic and clinical progression

KEYNOTE-001 Part D

The disposition of patients from randomisation through to database cut-off (April 2014) is presented in Figure 7 below:

Figure 7: CONSORT diagram – KEYNOTE-001 Part D



**Unknown = A disposition record did not exist at the time of reporting. All patients with unknown disposition status are still on study at the time of database cut-off.*

4.5.2 Characteristics of participants at baseline for each trial

KEYNOTE-006[18;23]

The study was stratified by line of therapy (first vs. second), PD-L1 status (high positive vs. low positive) and ECOG status (0 vs. 1). The characteristics of patients at baseline in KEYNOTE-006 were well balanced across the treatment arms (Table 17).

Table 17: KEYNOTE-006 - Patient baseline demographics and disease characteristics (ITT population)[18;23]

	Pembrolizumab 10 mg/kg Q2W n = 279	Pembrolizumab 10 mg/kg Q3W n = 277	Ipilimumab 3 mg/kg Q3W n = 278
Median age (range) — year	61 (18-89)	63 (22-89)	62 (18-88)
Sex — no. (%)			
• Male	161 (57.7)	174 (62.8)	162 (58.3)
• Female	118 (42.3)	103 (37.2)	116 (41.7)
Race — no. (%)			
• White	273 (97.8)	271 (97.8)	272 (97.8)
• Non-white or multiple	4 (1.4)	5 (1.8)	6 (2.2)
• Not reported	2 (0.7)	1 (0.4)	0 (0.0)
Region of enrolment — no. (%)			
• US	50 (17.9)	47 (17.0)	64 (23.0)
• Ex-US	229 (82.1)	230 (83.0)	214 (77.0)
ECOG performance status — no. (%)			
• 0	196 (70.3)	189 (68.2)	188 (67.6)
• 1	83 (29.7)	88 (31.8)	90 (32.4)
Baseline LDH level — no. (%)			
• Normal	193 (69.2)	175 (63.2)	178 (64.0)
• Elevated	81 (29.0)	98 (35.4)	91 (32.7)
• Missing	5 (1.8)	4 (1.4)	9 (3.2)
Median baseline tumour burden (range) — mm	57.5 (11-390)	61.7 (11-554)	55.2 (10-465)
Metastasis stage — no. (%)			
• M0	9 (3.2)	9 (3.2)	14 (5.0)
• M1*	6 (2.2)	4 (1.4)	5 (1.8)
• M1a	21 (7.5)	34 (12.3)	30 (10.8)
• M1b	64 (22.9)	41 (14.8)	52 (18.7)
• M1c	179 (64.2)	189 (68.2)	177 (63.7)
PD-L1 expression — no. (%)			
• Positive	225 (80.6)	221 (79.8)	225 (80.9)
• Negative	49 (17.6)	54 (19.5)	47 (16.9)

• Missing	5 (1.8)	2 (0.7)	6 (2.2)
PD-L1 Status			
• PD-L1 low	49 (17.6)	53 (19.1)	46 (16.5)
• PD-L1 high	219 (78.5)	217 (78.3)	223 (80.2)
• Missing	11 (3.9)	7 (2.5)	9 (3.2)
BRAF status — no. (%)			
• Mutant	98 (35.1)	97 (35.0)	107 (38.5)
• Wild type	177 (63.4)	178 (64.3)	170 (61.2)
• Not determined	4 (1.4)	2 (0.7)	1 (0.4)
Brain metastasis — no. (%)	23 (8.2)	27 (9.7)	28 (10.1)
Lines of prior systemic therapy — no. (%)			
• 0	183 (65.6)	185 (66.8)	181 (65.1)
• 1	96 (34.4)	91 (32.9)	97 (34.9)
• 2	0 (0.0)	1 (0.4)	0 (0.0)
Type of prior systemic therapy - no. (%)			
• Adjuvant/ • neoadjuvant	42 (15.1)	30 (10.8)	36 (12.9)
• Prior chemotherapy†	36 (12.9)	41 (14.8)	29 (10.4)
• Prior immunotherapy†	8 (2.9)	7 (2.5)	12 (4.3)
• Prior BRAF and/or MEK inhibitor†	50 (17.9)	45 (16.2)	56 (20.1)

**Further classification of metastasis stage not provided.*
†For advanced or metastatic disease.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PDL1, programmed death receptor ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks.

KEYNOTE-001 (Part D)[70]

Table 18: KEYNOTE-001 Part D - Patients characteristics in Part D (APaT population)

	Pembrolizumab 2 mg/kg Q3W n = 51	Pembrolizumab 10 mg/kg Q3W n = 52
Median age (range) — year	60 (35-80)	60 (26-78)
Sex — no. (%)		
• Male	32 (62.7)	31 (59 .6)
• Female	19 (37.3)	21 (40.4)
Race — no. (%)		
• Asian	1 (2.0)	2 (3.8)
• Black or African American	0 (0.0)	1 (1.9)
• White	50 (98.0)	49 (94.2)
ECOG performance status — no. (%)		
• 0	41 (80.4)	46 (88.5)
• 1	10 (19.6)	6 (11.5)

Baseline LDH level — no. (%)		
• Normal	30 (58.8)	35 (67.3)
• Elevated	21 (41.2)	15 (28.8)
• Missing	0 (0.0)	2 (3.8)
Median baseline tumour burden (range) — mm	79 (13-404)	90 (16-358)
Metastasis stage — no. (%)		
• M0	1 (2.0)	0 (0.0)
• M1a	6 (11.8)	2 (3.8)
• M1b	12 (23.5)	8 (15.4)
• M1c	32(62.7)	42 (80.8)
BRAF status — no. (%)		
• Mutant	20 (39.2)	16 (30.8)
• Wild type	31 (60.8)	36 (69.2)
Brain metastasis — no. (%)	1 (2.0)	5 (9.6)
Lines of prior systemic therapy — no. (%)		
• 0	23 (45.1)	29 (55.8)
• 1	17 (33.3)	15 (28.8)
• 2	10 (19.6)	8 (15.4)
• 3 or more	1 (2.0)	0 (0.0)

4.6 *Quality assessment of the relevant randomised controlled trials*

Table 19: Quality assessment results for parallel group RCTs

Trial	KEYNOTE-006	KEYNOTE- 001 (Part D)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	N/A	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No
Were there any unexpected imbalances in drop-outs between groups?	Yes	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

KEYNOTE-006

The write up in this section focuses on the findings in the pembrolizumab 10 mg/kg Q3W arm versus ipilimumab, as the Q3W dosing schedule is likely to be the licensed dosing schedule of pembrolizumab.

For completeness, results are presented for both pembrolizumab 10 mg/kg study arms (Q3W and Q2W) in the tables and figures included in this section.

Summary:

KEYNOTE-006[18;23] is an international, randomised, open-label phase 3 study of pembrolizumab versus ipilimumab for the treatment of patients with advanced (unresectable stage III or IV) melanoma who were naïve to prior ipilimumab therapy.

Enrolment occurred between September 2013 and March 2014. On 24 March 2015, MSD announced that KEYNOTE-006 had met its two primary endpoints of PFS and OS, and would be stopped early. Pembrolizumab was shown to be statistically superior to ipilimumab for PFS, OS, and ORR. Data from the study was presented in the opening plenary session at the American Association of Cancer Research (AACR) annual meeting on 19 April 2015, and also published on the same day in the New England Journal of Medicine.[18] The study will continue safety and survival follow-up until the final analysis.

All data presented below are from IA1 (data cut-off September 2014) with the exception of OS data which is from IA2 (data cut-off March 2015)

An overview of the study population is provided in Table 20 below:

Table 20: KEYNOTE-006 - study population

	Ipilimumab 3mg/kg Q3W n	Pembrolizumab 10 mg/kg Q3W n	Pembrolizumab 10 mg/kg Q2W n	Total n
Randomised patients (ITT population)	278	277	279	834
All Patients as Treated (APaT)	256	277	278	811
(Database cut-off date: 03SEP2014)				

A summary of the clinical efficacy outcome results based on IA1 (PFS and ORR) and IA2 (OS only) for pembrolizumab versus ipilimumab are presented in Table 21 below:

Table 21: KEYNOTE-006 – Key efficacy outcomes

	Control (ipilimumab) (n=278)	Pembrolizumab 10 mg/kg Q3W (n=277)	Pembrolizumab 10 mg/kg Q2W (n=279)
PFS by IRO based on RECIST 1.1 (IA1)			
Hazard Ratio (95% CI)		0.58 (0.47, 0.72)	0.58 (0.46, 0.72)
p-Value†		<0.00001	<0.00001
Median PFS (95% CI)	2.8 (2.8, 2.9)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)
PFS Rate at Month 6 in % (95% CI)	26.5 (20.9, 32.4)	46.4 (40.3, 52.3)	47.3 (41.2, 53.2)
OS (1A2)			
Hazard Ratio (95% CI)		0.69 (0.52, 0.90)	0.63 (0.47, 0.83)
p-Value†		0.00358	0.00052
Median OS (95% CI)	Not Reached (12.7, .)	Not Reached (., .)	Not Reached (., .)
OS Rate at Month 6 in % (95% CI)	74.5 (68.7, 79.4)	87.3 (82.7, 90.7)	84.8 (80.0, 88.5)
ORR by IRO based on RECIST 1.1 (IA1)			
Number of Responders; Overall Response Rate (%) (95% CI)	33 11.9% (8.3, 16.3)	91 32.9% (27.4, 38.7)	94 33.7% (28.2, 39.6)
Difference in % vs. Control Estimate (95% CI)		17.2 (9.5, 25.6)	16.1 (7.8, 24.5)
p-Value†		0.00002	0.00013

Data cut-off date: 03SEP2014
IA1 – Interim-analysis 1; IA2 = Interim-analysis 2
†One-sided p-value.
p-value for PFS and OS is based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs. 2nd), PD-L1 status (high positive vs. low positive) and ECOG (0 vs. 1).
p-value for ORR is based on Miettinen & Nurminen method stratified by line of therapy (1st vs. 2nd), PD-L1 status (high positive vs. low positive) and ECOG (0 vs. 1).

Efficacy results are presented in more detail below:

Primary Endpoints

PFS: IA1 (data cut-off 03 September 2014)

- *PFS analyses based on central (IRO) evaluation using RECIST 1.1 (ITT population)*

Treatment with pembrolizumab was associated with a statistically significant improvement in PFS compared to ipilimumab at the pre-specified 0.002 alpha level. Table 22 and Figure 8 summarise the primary analysis of PFS based on central review (i.e. images and selected

clinical data [e.g. skin photography, results of biopsies, if done, etc.] were submitted to an independent review committee, and were evaluated by 2 independent radiologists [and an adjudicator if needed]. Clinical data was integrated into the assessment by an independent oncologist. Together this comprised independent radiologists and oncologist [IRO] review).

Based on a total of 502 PFS events among three arms, the HR was 0.58 in both pembrolizumab arms over the control arm (the one-sided p-value was p<0.00001 in both comparisons, favouring pembrolizumab, which is statistically significant at the pre-specified alpha of 0.002 and meets the pre-specified criterion for a positive study). The median follow up time was 7.9 months for IA1. There was no statistical difference in PFS between the two pembrolizumab study arms with different dosing schedules (HR=0.97, p=0.76 for comparison of the two pembrolizumab arms). The median PFS was improved in the pembrolizumab arms compared to ipilimumab; specifically 4.1 months in the pembrolizumab 10 mg/kg Q3W arm, and 2.8 months in the control arm (Table 22). The PFS curves show a definite separation after the time of the first assessment (12 weeks), and the separation increased thereafter, reflected by a 6 month PFS rate of 46.4% (95% CI; 40.3%, 52.3%) in the pembrolizumab 10 mg/kg Q3W arm, compared to 26.5% (95% CI; 20.9%, 32.4%) in the ipilimumab arm (Table 22, Figure 8).

Table 22: KEYNOTE-006 - Analysis of PFS based on central (IRO) assessment - primary censoring rule (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Ipilimumab 3mg/kg	278	188 (67.6)	910.9	20.6	2.8 (2.8, 2.9)	26.5 (20.9, 32.4)	---	---
Pembrolizumab 10 mg/kg Q3W	277	157 (56.7)	1303.1	12.0	4.1 (2.9, 6.9)	46.4 (40.3, 52.3)	0.58 (0.47, 0.72)	0.00000
Pembrolizumab 10 mg/kg Q2W	279	157 (56.3)	1334.4	11.8	5.5 (3.4, 6.9)	47.3 (41.2, 53.2)	0.58 (0.46, 0.72)	0.00000
Pairwise Comparison							**Hazard Ratio‡ (95% CI)‡**	**p-Value‖**
Pembrolizumab 10 mg/kg Q2W vs. Pembrolizumab 10 mg/kg Q3W							0.97 (0.77, 1.21)	0.75869

IRO: Independent Radiology plus Oncologist Review.
Progression-free survival is defined as time from randomisation to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs. 2nd), PD-L1 status (high positive vs. low positive) and ECOG (0 vs. 1).
§ One-sided p-value based on log-rank test.
‖ Two-sided p-value based on log-rank test.
(Database cut-off date: 03SEP2014)

Figure 8: KEYNOTE-006 - KM of PFS based on central (IRO) assessment - primary censoring rule (ITT population)[18]

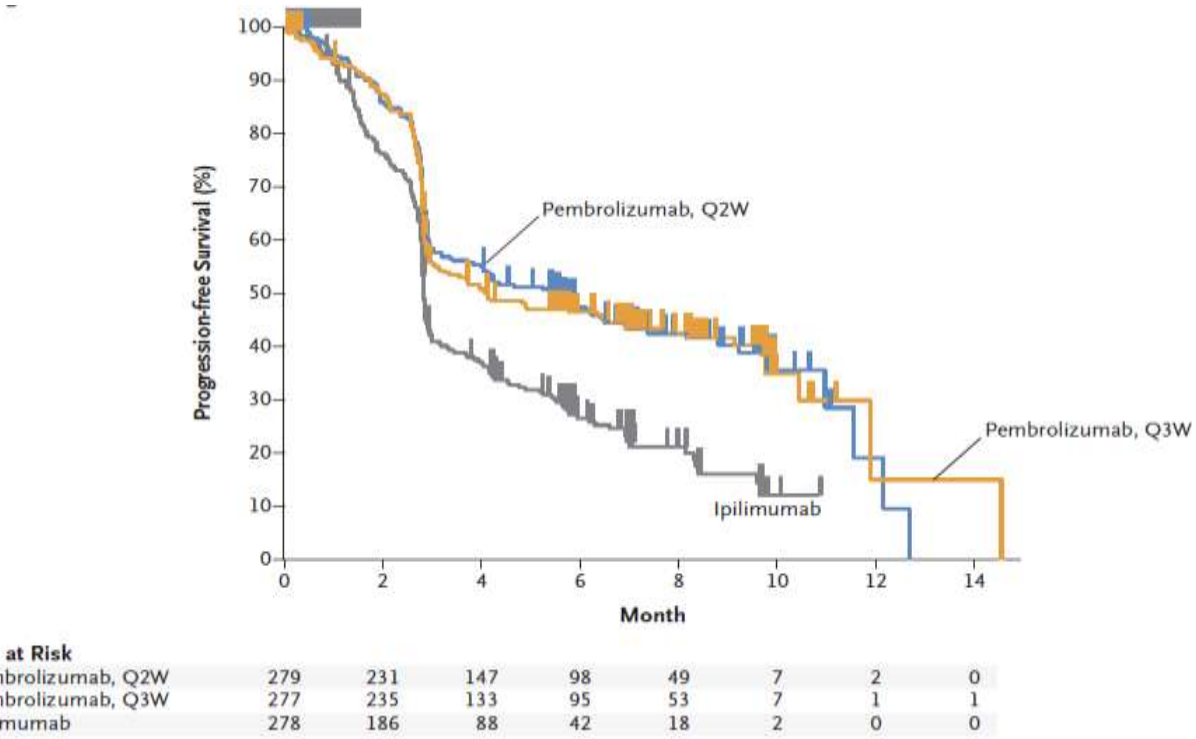


Table 23 provides the PFS rate over time based on central review using RECIST 1.1. The analysis indicates that PFS is superior for pembrolizumab by treatment arm compared to ipilimumab at every time point analysed.

Table 23: KEYNOTE-006 - PFS rate over time based on central (IRO) assessment per RECIST 1.1 (ITT population)

	Ipilimumab 3 mg/kg (n=278)	Pembrolizumab 10 mg/kg Q3W (n=277)	Pembrolizumab 10 mg/kg Q2W (n=279)
PFS Rate at 3 months in %† (95% CI)	*40.9 (34.7, 47.0)*	*55.7 (49.5, 61.4)*	*58.3 (52.2, 64.0)*
PFS Rate at 6 months in %† (95% CI)	*26.5 (20.9, 32.4)*	*46.4 (40.3, 52.3)*	*47.3 (41.2, 53.2)*
PFS Rate at 9 months in %† (95% CI)	*16.0 (10.3, 22.7)*	*41.6 (35.3, 47.8)*	*40.3 (33.6, 46.8)*
PFS Rate at 12 months in %† (95% CI)	---	*14.9 (1.7, 41.0)*	*19.0 (5.3, 39.0)*

IRO: Independent Review Committee + Oncologist review
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From the product-limit (Kaplan-Meier) method for censored data.
(Database cut-off Date: 03SEP2014)

- *PFS analyses based on Investigator (INV) assessment using irRC (ITT population)*

The PFS results were consistent between independent central evaluation (IRO per RECIST 1.1) and INV evaluation (per irRC).

In applying the irRC, the protocol allowed subjects to stay on study treatment until progression of disease was confirmed on a subsequent tumor assessment if they met specific criteria. This approach allowed physicians to manage subjects by using an approach more suitable to immunotherapies such as pembrolizumab and ipilimumab. PFS analysis by irRC was performed by considering an event to be progressive disease (PD) only if it was confirmed at the next assessment, approximately 4 weeks later, unless there was no subsequent assessment or the subsequent assessment was not evaluable or not assessable after the progressive disease, e.g., by investigator discretion if the subject was not clinically stable. Therefore subjects who had a single assessment of PD followed by a non-PD assessment, were not considered to have a progression event. When PD was confirmed, the date of initial progression was used as the time of progression.

Table 24 and Figure 9 summarise PFS based on INV assessment. Based on a total of 464 PFS events among three arms, the HR was 0.56 in both pembrolizumab arms over the control arm, respectively ($p<0.00001$ in both comparisons, favouring pembrolizumab). The median PFS was 7.2 months in the pembrolizumab 10 mg/kg Q3W arm, and 3.3 months in the control arm. The KM estimate of PFS (Figure 9) reveals a pattern of PFS curves that is similar to the primary PFS analysis, with the difference in the PFS rate persisting beyond 6 months, reflected by a 6-month PFS rate of 55.0% (95% CI; 48.8%, 60.7%) in the pembrolizumab 10 mg Q3W arm, compared to 33.6% (95% CI; 27.6%, 39.7%) in the ipilimumab arm (Table 24 and Figure 9).

Table 24: KEYNOTE-006 - Analysis of PFS based on INV assessment per irRC - primary censoring rule (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median PFS[†] (Months) (95% CI)	PFS Rate at Month 6 in % [†] (95% CI)	Treatment vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Ipilimumab 3mg/kg	278	177 (63.7)	1047.0	16.9	3.3 (2.9, 4.2)	33.6 (27.6, 39.7)	---	---
Pembrolizumab 10 mg/kg Q3W	277	145 (52.3)	1486.9	9.8	7.2 (5.6, 9.7)	55.0 (48.8, 60.7)	0.56 (0.45, 0.70)	0.00000
Pembrolizumab 10 mg/kg Q2W	279	142 (50.9)	1468.1	9.7	7.0 (5.6, 9.6)	54.5 (48.3, 60.3)	0.56 (0.45, 0.70)	0.00000
Pairwise Comparison							Hazard Ratio[‡]	p-Value[ǁ]

	(95% CI)‡	
Pembrolizumab 10 mg/kg Q2W vs. Pembrolizumab 10 mg/kg Q3W	1.01 (0.80, 1.27)	0.95835

Progression-free survival is defined as time from randomisation to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs. 2nd), PD-L1 status (high positive vs. low positive) and ECOG (0 vs. 1); if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

§ One-sided p-value based on log-rank test.

‖ Two-sided p-value based on log-rank test.

(Database cut-off date: 03SEP2014)

Figure 9: KEYNOTE-006 - KM of PFS based on INV assessment per irRC - primary censoring rule (ITT population)

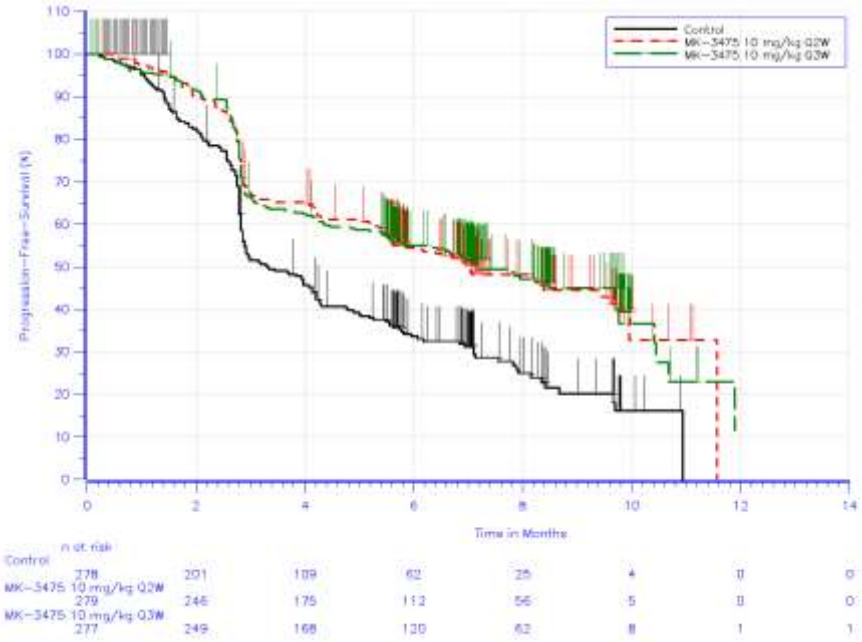


Table 25 provides the PFS rate over time based on INV assessment using irRC. The analysis indicates that PFS is superior for pembrolizumab compared to ipilimumab at every time point.

Table 25: KEYNOTE-006 - PFS rate over time based on INV assessment per irRC (ITT population)

	Ipilimumab 3 mg/kg (n=278)	Pembrolizumab 10 mg/kg Q3W (n=277)	Pembrolizumab 10 mg/kg Q2W (n=279)
PFS Rate at 3 months in %† (95% CI)	*51.5 (45.0, 57.6)*	*66.5 (60.5, 71.7)*	*67.4 (61.5, 72.6)*
PFS Rate at 6 months in %† (95% CI)	*33.6 (27.6, 39.7)*	*55.0 (48.8, 60.7)*	*54.5 (48.3, 60.3)*
PFS Rate at 9 months in %† (95% CI)	*20.2 (14.0, 27.2)*	*45.1 (38.1, 51.8)*	*44.4 (37.4, 51.2)*
PFS Rate at 12 months	---	*11.5 (1.3, 34.0)*	---

in %† (95% CI)			
Progression-free survival is defined as time from randomisation to disease progression, or death, whichever occurs first. *† From the product-limit (Kaplan-Meier) method for censored data.* *(Database Cutoff Date: 03SEP2014)*			

OS: IA1 (data cut-off 03 September 2014) and IA2 (data cut-off 03 March 2015)

- *OS analyses –IA1*

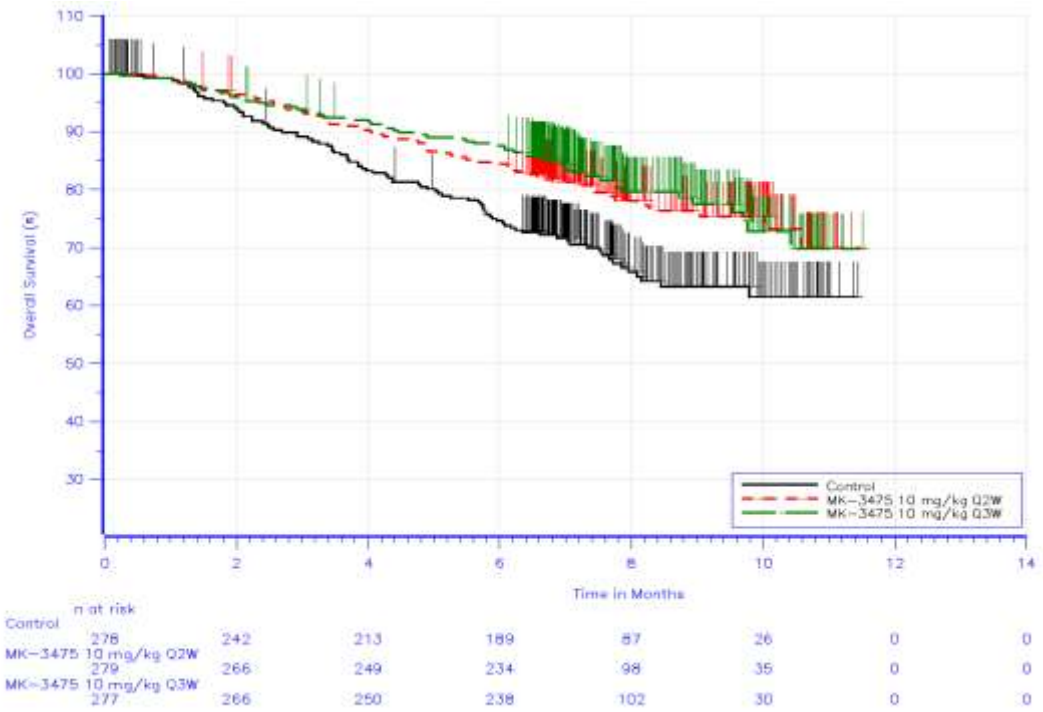
Overall survival analysis was conducted at IA1 as planned. A total of 202 patients died, representing 46% of the target number of events at final analysis (435 deaths). At IA1, the HR for OS was 0.56 (p =0.00031) in the pembrolizumab 10 mg/kg Q3W arm, favouring pembrolizumab. None of the medians were reached (Table 26 and Figure 10). The 6-month OS rates were 87.6% (95% CI; 83.1%, 91.0%) in the pembrolizumab 10 mg/kg Q3W arm, and 74.6% (95% CI; 68.8%, 79.5%) in the ipilimumab arm. Both pembrolizumab treatment arms demonstrated similar OS to each other (HR=1.09, p=0.65 for comparison of the two pembrolizumab treatment arms).

Table 26: KEYNOTE-006 - Analysis of OS at IA1 (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in % † (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Ipilimumab 3mg/kg	278	85 (30.6)	1767.4	4.8	Not Reached (., .)	74.6 (68.8, 79.5)	---	---
Pembrolizumab 10 mg/kg Q3W	277	56 (20.2)	2043.1	2.7	Not Reached (., .)	87.6 (83.1, 91.0)	0.56 (0.40, 0.78)	0.00031
Pembrolizumab 10 mg/kg Q2W	279	61 (21.9)	2034.9	3.0	Not Reached (., .)	84.8 (80.0, 88.5)	0.60 (0.43, 0.84)	0.00132
Pairwise Comparison							**Hazard Ratio‡ (95% CI)‡**	**p-Value‖**
Pembrolizumab 10 mg/kg Q2W vs. Pembrolizumab 10 mg/kg Q3W							1.09 (0.76, 1.57)	0.64533

Subjects who had survival follow-up after data cutoff date have been censored at date of data cutoff
† From product-limit (Kaplan-Meier) method for censored data.
† From product-limit (Kaplan-Meier) method for censored data. if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
§ One-sided p-value based on log-rank test.
‖ Two-sided p-value based on log-rank test.
(Database cut-off date: 03SEP2014)

Figure 10: KEYNOTE-006 - KM of OS at IA1 (ITT population)



Despite a striking treatment effect, the OS was not statistically significant at the pre-specified alpha level of 0.00002 at IA1 that would have warranted early stopping for efficacy. With an OS rate of ~82% at 6 months across the 3 arms, the OS data was not mature at IA1 which had a median OS follow-up of ~8 months. The study therefore continued survival follow up as recommended by the DMC. An interim OS analysis (IA2) was subsequently performed when as pre-specified in the study protocol.

OS results for pembrolizumab at IA2 were found to be statistically significant versus ipilimumab, as presented below:

- *OS analyses –IA2*

The primary objective of IA2 was to evaluate treatment effect based on OS. The IA2 was driven by 12 months of follow-up because the number of deaths was <290. A total of 289 patients died, representing 66% of the target number of events at final analysis (435 deaths). Patients who had a survival update after the IA2 data cut-off date of 03 March 2015 were censored on 03 March 2015 in this OS analysis. OS was found to be statistically significant in both pembrolizumab arms at the pre-specified alpha level of 0.005 using the Hochberg step-up procedure at IA2. The HR for OS was 0.69 (p=0.00358) in the pembrolizumab 10 mg/kg Q3W arm over the ipilimumab arm, favouring pembrolizumab (Table 27 and

Figure 11). OS between the two pembrolizumab arms was also shown to be comparable (HR 0.91, p=0.51319). At the time of IA2, the median OS had not been reached for all three arms. The median follow-up time at IA2 was 13.85 months.

The 6-month OS rates were 87.3% (95% CI; 82.7%, 90.7%) for pembrolizumab 10 mg/kg Q3W, compared to 74.5% (95% CI; 68.7%, 79.4%) in the ipilimumab arm (see Table 27). Table 28 provides further results of OS rates at different time-points. At 12 months, survival rates were improved by about 10% for subjects receiving pembrolizumab 10 mg/kg Q3W compared to ipilimumab (12 month OS rate of 58.2% (95% CI: 51.8, 64.0) for the ipilimumab arm, and 68.4% (95% CI: (62.5, 73.6) for the pembrolizumab 10 mg/kg Q3W arm).

Table 27: KEYNOTE-006 - Analysis of OS at IA2 (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in % † (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Ipilimumab 3mg/kg	278	112 (40.3)	2572.3	4.4	Not Reached (12.7, .)	74.5 (68.7, 79.4)	---	---
Pembrolizumab 10 mg/kg Q3W	277	92 (33.2)	3105.7	3.0	Not Reached (., .)	87.3 (82.7, 90.7)	0.69 (0.52, 0.90)	0.00358
Pembrolizumab 10 mg/kg Q2W	279	85 (30.5)	3152.8	2.7	Not Reached (., .)	84.8 (80.0, 88.5)	0.63 (0.47, 0.83)	0.00052

Pairwise Comparison	Hazard Ratio‡ (95% CI)‡	p-Value‖
Pembrolizumab 10 mg/kg Q2W vs. Pembrolizumab 10 mg/kg Q3W	0.91 (0.67, 1.22)	0.51319

Subjects who had survival follow-up after data cutoff date have been censored at date of data cutoff (03MAR2015)

† From product-limit (Kaplan-Meier) method for censored data.

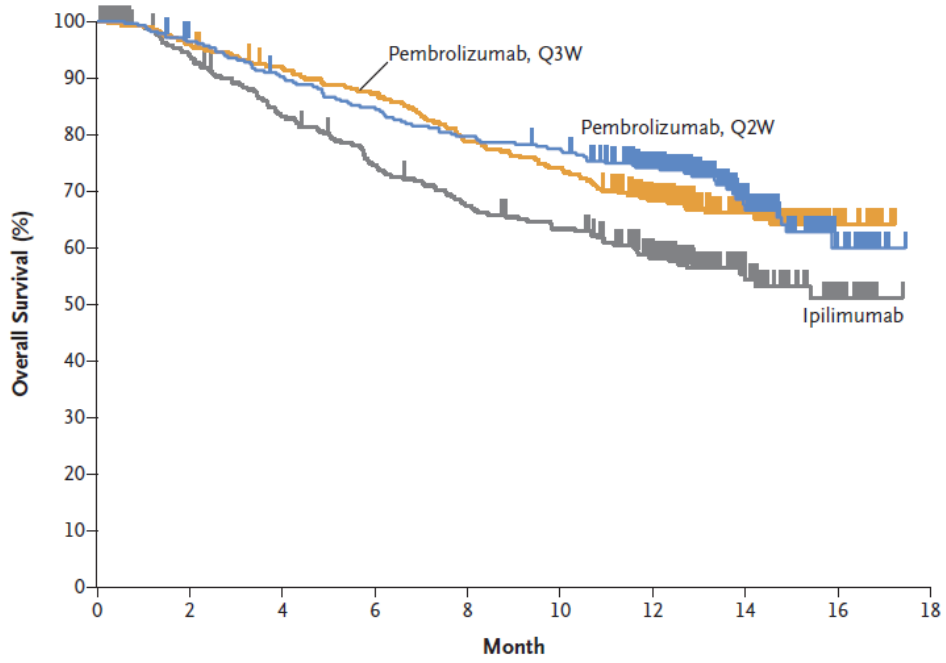
‡ Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs. 2nd), PD-L1 status (positive vs. negative) and ECOG (0 vs. 1); if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

§ One-sided p-value based on log-rank test.

‖ Two-sided p-value based on log-rank test.

(Database cut-off date: 03MAR2015)

Figure 11: KEYNOTE-006 - KM of OS at IA2 (ITT population)[18]



No. at Risk										
Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

Table 28: KEYNOTE-006 - OS Rate at 4, 6, 12 and 15 Months (ITT Population)

	Ipilimumab 3 mg/kg Q3W	Pembrolizumab 10 mg/kg Q3W	Pembrolizumab 10 mg/kg Q2W	Pembrolizumab combined
	(N=278)	(N=277)	(N=279)	(N=556)
OS Rate at 4 Months in % (95% CI)†	83.2 (78.0, 87.3)	92.0 (88.1, 94.7)	90.2 (86.1, 93.2)	91.1 (88.4, 93.2)
OS Rate at 6 Months in % (95% CI)†	74.5 (68.7, 79.4)	87.3 (82.7, 90.7)	84.8 (80.0, 88.5)	86.0 (82.8, 88.7)
OS Rate at 12 Months in % (95% CI)†	58.2 (51.8, 64.0)	68.4 (62.5, 73.6)	74.1 (68.5, 78.9)	71.3 (67.3, 74.9)
OS Rate at 15 Months in % (95% CI)†	53.1 (45.9, 59.7)	64.0 (57.3, 69.9)	62.8 (54.8, 69.7)	63.4 (58.2, 68.0)
Subjects who had survival follow-up after data cutoff date have been censored at date of data cutoff (03MAR2015) (Database cut-off date: 03MAR2015)				

After reviewing the results of IA2, the DMC recommendations were for IA2 to be the definitive OS analysis; to stop the study early and unblind the study; to continue to follow for OS; and to make pembrolizumab available to the subjects with PD that had been on the ipilimumab arm.

As OS was positive at IA2, no formal OS analysis will be conducted at the planned final analysis. However, patients will continue to be followed up and long-term survival for this study will be updated as deemed appropriate.

Secondary Endpoints

ORR: IA1 (data cut-off 03 September 2014)

- *ORR – Central (IRO) assessment per RECIST 1.1 - ITT population*

The primary method of analysis of ORR was based on independent central review (IRO assessment) of response using RECIST 1.1 and results are summarised in Table 29.

At IA1, both pembrolizumab arms demonstrated superiority to ipilimumab in PFS at one-sided alpha of 0.002; ORR was sequentially tested for each pembrolizumab arm. The one-sided p-value was <0.001 for each pembrolizumab arm versus the ipilimumab arm in ORR, demonstrating superiority to ipilimumab in ORR.

Pembrolizumab demonstrated a markedly higher confirmed objective response rate compared to ipilimumab. Improvement of ORR with pembrolizumab is approximately 3 fold, and the difference is statistically significant. The ORR was 32.9% in the pembrolizumab 10 mg/kg Q3W arm, and 11.9% in the ipilimumab control arm based on central (IRO) review.

Table 29: KEYNOTE-006 - Analysis of ORR based on central (IRO) assessment per RECIST 1.1 (ITT Population)

Treatment	N	Number of Overall Responses	Overall Response	Difference in % vs. Control	
			Rate (%) (95% CI)	Estimate (95% CI)†	p-Value††
Ipilimumab 3mg/kg	278	33	11.9 (8.3, 16.3)		.
Pembrolizumab 10 mg/kg Q3W	277	91	32.9 (27.4, 38.7)	17.2 (9.5,25.6)	0.00002
Pembrolizumab 10 mg/kg Q2W	279	94	33.7 (28.2, 39.6)	16.1 (7.8,24.5)	0.00013
Pairwise Comparison				**Estimate (95% CI)†**	**p-Value§**
Pembrolizumab 10 mg/kg Q2W vs. Pembrolizumab 10 mg/kg Q3W				-1.1 (-10.6, 8.6)	0.82636

IRO = Independent Radiologist plus Oncologist Review
Responses are based on IRO global radiological and oncologist assessments per RECIST 1.1 with confirmation.
† Based on Miettinen & Nurminen method stratified by line of therapy (1st vs. 2nd), PD-L1 status (high positive vs. low positive) and ECOG (0 vs. 1); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
§ Two-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % ≠ 0.
(Database cut-off date: 03SEP2014)

Table 30 summarises the best response results by central (IRO) assessment using RECIST 1.1. There were 17 (6.1%) CRs in the pembrolizumab 10 mg/kg Q3W arm compared to 4 (1.4%) CRs in the ipilimumab arm. The disease control rate (CR+PR+SD) was 52.0% (144

subjects) in the pembrolizumab 10 mg/kg Q3W arm, and 32.0% (89 subjects) in the ipilimumab arm.

Table 30: Summary of best response based on central (IRO) assessment per RECIST 1.1 (ITT population)

	Ipilimumab 3 mg/kg		Pembrolizumab 10 mg/kg Q3W		Pembrolizumab 10 mg/kg Q2W	
	n	(%)	n	(%)	n	(%)
Number of Subjects in Population	278		277		279	
Complete Response (CR)	4	(1.4)	17	(6.1)	14	(5.0)
Partial Response (PR)	29	(10.4)	74	(26.7)	80	(28.7)
Overall Response (CR+PR)	**33**	**(11.9)**	**91**	**(32.9)**	**94**	**(33.7)**
Stable Disease (SD)	46	(16.5)	39	(14.1)	37	(13.3)
NonCR/NonPD (NN)	10	(3.6)	14	(5.1)	13	(4.7)
Disease Control (CR+PR+SD+NN)	**89**	**(32.0)**	**144**	**(52.0)**	**144**	**(51.6)**
Progressive Disease (PD)	136	(48.9)	114	(41.2)	106	(38.0)
Not Evaluable	51	(18.3)	15	(5.4)	20	(7.2)
No Assessment	2	(0.7)	4	(1.4)	9	(3.2)

IRO = Independent Review Committee + Oncologist Review
Responses are based on IRO best assessment across timepoints.
(Database cut-off date: 03SEP2014)

- *ORR – INV assessment per irRC - ITT population*

The ORR results based on INV assessment using irRC were similar to the ORR analysis based on central (IRO) assessment: pembrolizumab showed clear superiority to ipilimumab. The ORR based on INV assessment per irRC was 37.5% in the pembrolizumab 10 mg/kg Q3W arm, (37.3% in the pembrolizumab 10 mg/kg Q2W), and 16.2% in the ipilimumab arm. The one-sided p-value was <0.0001 for both pembrolizumab arms.[23]

Time to response and response duration: IA1 (data cut-off 03 September 2014)

A summary of time to response and response duration for subjects achieving an objective response by central (IRO) or INV assessment for each treatment arm is provided in Table 31. Response duration is defined as the time from the first confirmed CR/PR to documented PD. Subjects who did not have PD were censored at the time of last disease response assessment.

The first scheduled disease assessment occurred at week 12 (around day 84), as indicated by the median times to response across the three treatment arms. Of interest, late responses to pembrolizumab and ipilimumab were observed across all study arms, with objective responses first recorded as late as 251 and 250 days in the pembrolizumab 10 mg/kg Q3W and ipilimumab arms respectively.

At the time of IA1, the median response duration could not be estimated, due to the fact that most of the responses were ongoing in each arm (~90%).

Table 31: KEYNOTE-006 - Summary of Time to Response and Response Duration for Subjects with Objective Response (ITT Population)

	Ipilimumab 3 mg/kg	Pembrolizumab 10 mg/kg Q3W	Pembrolizumab 10 mg/kg Q2W	Pembrolizumab combined
	(N=278)	(N=277)	(N=279)	(N=556)
IRO Assessment per RECIST 1.1				
Number of Patients with Response†	33	91	94	185
Time to Response † (days) • Mean (SD) • Median (Range)	 106 (36) 87 (80-250)	 99 (35) 85 (36-251)	 95 (26) 86 (32-212)	 97 (31) 85 (32-251)
Response Duration‡ (days) • Median (Range)§	 Not reached (33+ - 239+)	 Not reached (42+ - 246+)	 251 (42+ - 251)	 251 (42+ - 251)
Number of Response Ongoing (%)	29 (88)	88 (97)	84 (89)	172 (93)
Investigator Assessment per irRC				
Number of Patients with Response†	45	104	104	208
Time to Response † (days) • Mean (SD) • Median (Range)	 108 (36) 87 (43-202)	 95 (25) 85 (58-212)	 98 (30) 86 (58-216)	 97 (28) 85 (58-216)
Response Duration‡ (days)				
• Median (Range)§	Not reached (33+ - 254+)	Not reached (42+ - 253+)	Not reached (29+ - 254+)	Not reached (29+ - 254+)
Number of Response Ongoing (%)	41 (91)	96 (92)	97 (93)	193 (93)

Independent Radiologist plus Oncologist Review.
IRC: Independent Review Committee.
† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
‡ From product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates there is no progressive disease by the time of last disease assessment.
(Database cut-off date: 03SEP2014)

Exploratory endpoints

Results concerning HRQoL exploratory endpoints are currently unavailable in the KEYNOTE-006 clinical study report (CSR) based on the data reported from IA1 and IA2. However internal analyses have been conducted and are reported in section 5.4.

KEYNOTE-001 - Part D: Data cut-off 18 April 2014

Summary

A summary of the key efficacy endpoints concerning Part D of KEYNOTE-001[70] is provided in Table 32 below:

Table 32: KEYNOTE-001 Part D (ipilimumab-naïve population) - Summary of key efficacy endpoints for pembrolizumab in advanced melanoma

	2 mg/kg Q3W	10 mg/kg Q3W
Number of Patients (FAS/APaT)	45/51	47/52
BOR Analysis (IRO per RECIST 1.1)		
ORR – FAS % (95% CI)	33% (20, 49)	38% (25, 54)
ORR – APaT % (95% CI)	33% (21, 48)	35% (22, 49)
Response Duration[1] (IRO per RECIST 1.1, APaT Population)		
Median in weeks	Not Reached	Not reached
% of responses ongoing among responders	82%	72%
Median Time to Response in Weeks (range)	12 (11-39)	12 (11-37)
PFS (IRO per RECIST 1.1, APaT Population)		
Median in months (95% CI)	5.5 (2.8, 14)	4.2 (2.8,9.9)
PFS rate at 6 months (%)	50%	41%
PFS (IRO per irRC, APaT Population with Confirmed Responders)		
Median in months (95% CI)	8.3 (3.4, 13.8)	6.3 (3.7, 11.3)
PFS rate at 6 months (%)	58%	51%
OS (APaT population)		
Median in months	Not reached	Not reached
12 month OS rate (%)	72%	64%

[1]*Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.*
Data cut-off date: 18APR2014.

Efficacy results are presented in more detail below:

Primary endpoints:

Response Rate (RR) – Part D FAS population

Best Overall Response (BOR) analysis as assessed by central review (IRO) using RECIST 1.1 is shown in Table 33 below. ORR is 36% (95% CI: 26-47%) in the FAS population across both dose arms, and does not differ substantially by dose of pembrolizumab. Disease control (stable disease or better) was reported in 52% of patients in the Part D FAS population, and again did not differ substantially by dose.

Table 33: KEYNOTE-001 Part D - Summary of best overall response based on central (IRO) assessment per RECIST 1.1 (FAS Population)

	Pembrolizumab 2mg/kg Q3W (N=45)			Pembrolizumab 10mg/kg Q3W (N=47)			Total (N=92)			Difference in Rate‡		p-Value‡
	N	%	95% CI †	N	%	95% CI †	n	%	95% CI †	%	95% CI	
Complete response (CR)	3	6.7	(1.4, 18.3)	4	8.5	(2.4, 20.4)	7	7.6	(3.1, 15.1)			
Partial response (PR)	12	26.7	(14.6, 41.9)	29.8	29.8	(17.3, 44.9)	26	28.3	(19.4, 38.6)			
Overall response (CR + PR)	**15**	**33.3**	**(20.0, 49.0)**	**18**	**38.3**	**(24.5, 53.6)**	**33**	**35.9**	**(26.1, 46.5)**	**-5.0**	**(-24.1, 14.7)**	**0.6216**
Stable disease (SD)	7	15.6	(6.5, 29.5)	8	17.0	(7.6, 30.8)	15	16.3	(9.4, 25.5)			
Disease control (CR+PR+SD)	**22**	**48.9**	**(33.7, 64.2)**	**26**	**55.3**	**(40.1, 69.8)**	**48**	**52.2**	**(41.5, 62.7)**	**-6.4**	**(-26.3, 13.9)**	**0.5393**
Progressive disease (PD)	19	42.2	(27.7, 57.8)	14	29.8	(17.3, 44.9)	33	35.9	(26.1, 46.5)			
Not evaluable (NE)	4	8.9	(2.5, 21.2)	7	14.9	(6.2, 28.3)	11	12.0	(6.1, 20.4)			

RECIST=Response Evaluation Criteria In Solid Tumours (version 1.1).
Only confirmed responses are included in this table.
† Based on binomial exact confidence interval method.
‡ From Miettinen and Nurminen's method. Two-sided p-Value for testing. H0: Difference = 0 versus H1: Difference ≠ 0.
Database cut-off date: 18APR2014

Secondary endpoints:

Disease Control Rate (DCR), Response Duration, PFS and OS – Part D (APaT population)

Disease Control Rate (DCR), response duration and PFS, and OS served as secondary endpoints in this population.

DCR results have been presented in Table 33 and response duration analysis is summarised in Table 34 below. Patients initiated treatment by 11-Jan-2013, and at the time of the data cut-off for this analysis (18-Apr-2014), had least 15 months of follow-up. Response duration ranged from 6+ to 61+ weeks across both arms and the median response duration was not reached for either arm. 33 patients had a confirmed objective response, and 48 patients had PD by central (IRO) review (Table 33) and 29 (83%) had non-PD at the time of the analysis.

Table 34: KEYNOTE-001 Part D- Summary of time to response and response duration - central (IRO) assessment per RECIST 1.1 in patients with confirmed response (APaT population)

	Pembrolizumab 2mg/kg Q3W (N=51)	Pembrolizumab 10 mg/kg Q3W (N=52)	Total (N=103)
Number of Patients with Response†	17	18	35
Time to Response† (weeks) • **Mean (SD)** • **Median (Range)**	 18 (10) 12 (11-39)	 17 (9) 12 (11-37)	 17 (9) 12 (11-39)
Response Duration‡ (weeks) • **Median (Range)§** • **Number of Non-progressing (non-PD) (%)**	 Not reached (7+ - 60+) 15 (88)	 Not reached (6+ - 61+) 14 (78)	 Not reached (6+ - 61+) 29 (83)

† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
‡ From product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates non-PD at the last assessment (censored).
Database cut-off date: 18APR2014

PFS - Part D (APaT population)

PFS for patients in Part D is shown in Table 35 below. Approximately 65%-71% of patients in Part D had a PFS event at the time of data analysis. The median PFS was 5.5 months and 4.2 months for the 2 mg/kg Q3W and 10 mg/kg Q3W treatment arms respectively. Although there was a 1-month difference in the median PFS between arms, the difference in PFS between treatment arms was not significant (HR = 0.87, p=0.5).

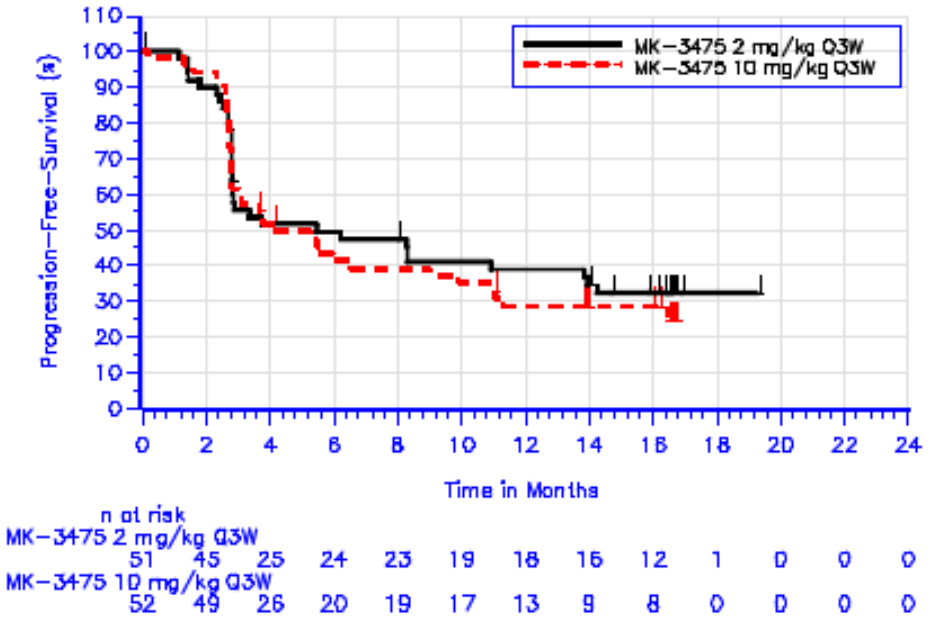
In Part D, the 6-month PFS rate was 50% for the 2 mg/kg Q3W arm and 41% for the 10 mg/kg Q3W arm by KM estimation. The PFS curves are similar between the two dose levels, (Figure 12). The PFS curves are overlapping between treatment arms. At both dose levels there is a sharp decline in the PFS curves around Week 12, which is consistent with the first imaging assessment time point, followed by a substantially reduced failure rate in PFS thereafter. Inspection of the PFS curves supports the durability of response to pembrolizumab treatment.

Table 35: KEYNOTE-001 Part D - Summary of PFS based on central (IRO) assessment per RECIST 1.1 (APaT population)

	Pembrolizumab 2 mg/kg Q3W (N=51)	Pembrolizumab 10 mg/kg Q3W (N=52)	Pembrolizumab 2 mg/kg Q3W vs. Pembrolizumab 10 mg/kg Q3W
			Hazard Ratio[†]; (95% CI); p-Value[‡]
Number (%) of PFS Events	33 (64.7)	37 (71.2)	
Person-Months	407	373	
Event Rate/100 Person-Months (%)	8.1	9.9	
Median PFS (Months)[§]; (95% CI)	5.5 (2.8, 14)	4.2 (2.8, 9.9)	0.87 (0.54,1.39) P=0.545
PFS rate at 3 months (%)[§]	55.7	59.6	
PFS rate at 6 months (%)[§]	49.5	41.4	

† Based on Cox regression model with treatment as a covariate (pembrolizumab 2 mg/kg Q3W versus pembrolizumab 10 mg/kg Q3W).
‡ Two-sided p-value based on log-rank test.
§ From product-limit (Kaplan-Meier) method for censored data.
(Database cut-off date: 18APR2014)

Figure 12: KEYNOTE-001 Part D - KM estimates of PFS based on central (IRO) review per RECIST 1.1 (APaT population)



Database Cutoff Date: 18APR2014

OS – Part D (APaT population)

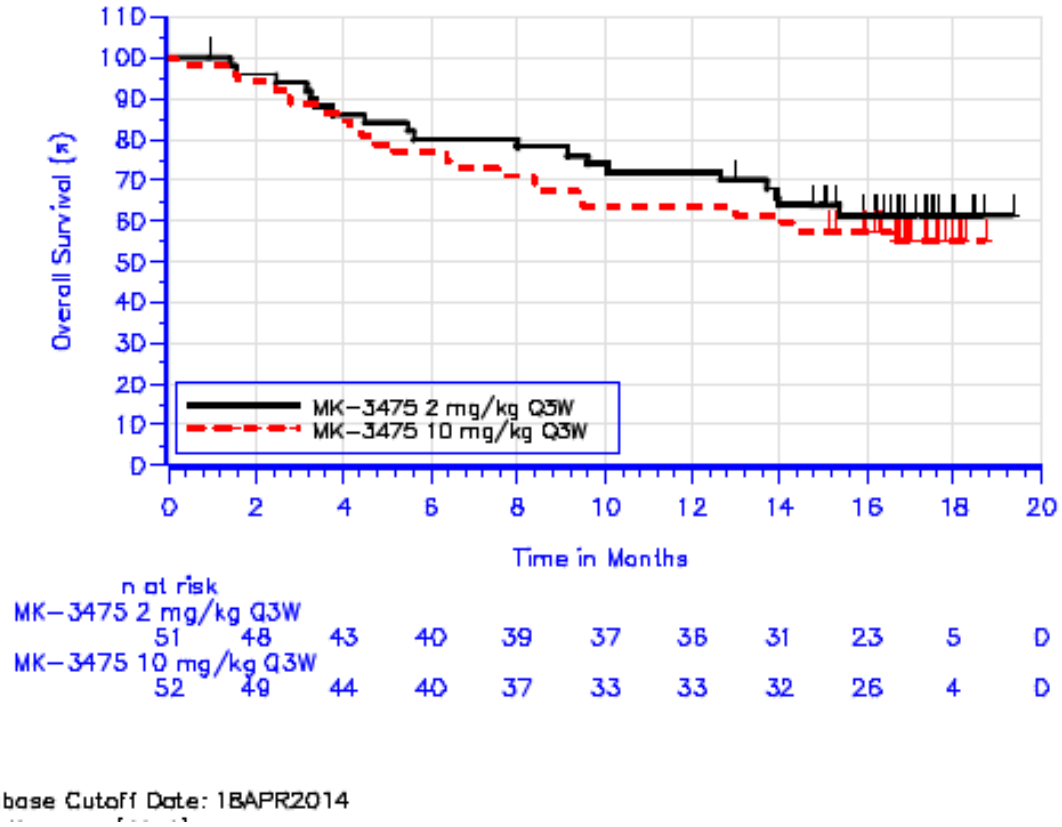
Overall survival for Part D ipilimumab-naïve patients is presented in Table 36 and Figure 13 below. Across both treatment arms, there were 42 deaths out of 103 patients. The median OS was not reached, and the lower bound of the 95% CI was 14.0 and 9.5, respectively, for the 2 mg/kg vs 10 mg/kg cohorts, respectively, to not estimable for both treatment arms. There was no significant difference in OS between treatment arms. The 12-month OS rate using the KM estimate for the 2 dose cohorts was 72% in the 2 mg/kg Q3W arm and 64% in the 10 mg/kg Q3W arm. The 18-month OS rate was 61% in the 2 mg/kg Q3W arm and 55% in the 10 mg/kg Q3W arm.

Table 36: KEYNOTE-001 Part D - Summary of OS (APaT population)

	Pembrolizumab 2 mg/kg Q3W (N=51)	Pembrolizumab 10 mg/kg Q3W (N=52)	Pembrolizumab 2 mg/kg Q3W vs. Pembrolizumab 10 mg/kg Q3W Hazard Ratio[†]; (95% CI); p-Value[‡]
Death (%)	19 (37.3)	23 (44.2)	
Median survival (months)[§]; (95% CI)	Not reached (14.0,.)	Not reached (9.5,.)	0. 81 (0.44,1.50) P=0.507
OS rate at 12 Months (%)[§]	72.0	63.5	
PFS rate at 18 Months (%)[§]	61.4	55.2	

OS: Overall survival.
† Based on Cox regression model with treatment as a covariate (pembrolizumab 2 mg/kg Q3W versus pembrolizumab 10 mg/kg Q3W).
‡ Two-sided p-value based on log-rank test.
§ From product-limit (Kaplan-Meier) method for censored data.
(Database cut-off date: 18APR2014)

Figure 13: KEYNOTE-001 Part D - KM estimates of OS based on central (IRO) review per RECIST 1.1 (APaT population)



Clinical data supporting the efficacy profile of the licensed dose and treatment schedule of pembrolizumab (2 mg/kg Q3W) in an ipilimumab-naïve patient population

KEYNOTE-006 considers two dosing regimens of pembrolizumab 10 mg/kg (Q2W and Q3W) versus ipilimumab in a melanoma patient population previously untreated with ipilimumab. Consequently, comparative data of the 2 mg/kg pembrolizumab dose versus ipilimumab in an ipilimumab-naïve advanced melanoma patient population is unavailable from KEYNOTE-006. Nevertheless, a direct comparison of the 2 mg/kg and 10 mg/kg doses is available from Part D of KEYNOTE-001 (n=103), which is specifically focused on the same patient population of interest. ORR, the primary efficacy endpoint for KEYNOTE-001, for the 2 mg/kg and 10 mg/kg Q3W doses was essentially identical in patients naïve to prior therapy with ipilimumab, at 33.3% and 34.6%, respectively (Table 32). Efficacy was also comparable between the two dose levels for the secondary efficacy endpoints of PFS and OS.

It is important to note that KEYNOTE-006 results demonstrate that the PFS (co-primary efficacy endpoint) outcomes for 10 mg/kg Q3W and 10 mg/kg Q2W doses were nearly identical, with overlapping KM curves (Figure 8; HR for the comparison of the two doses of 0.97 (p=0.76)), and 6-month PFS rates of 46% and 47%, respectively. The OS (co-primary efficacy endpoint) outcomes for 10 mg/kg Q3W and 10 mg/kg Q2W doses were also very similar in this study, with overlapping KM curves (

Figure **11**; HR for the comparison of the two doses of 0.91 (p=0.51)), and 12-month OS rates of 68% and 74%, respectively.

It is of particular interest to note the comparison of key efficacy endpoints in Part D of KEYNOTE-001 (ipilimumab-naïve melanoma comparing 2 mg/kg Q3W to 10 mg/kg Q3W) and KEYNOTE-006 (ipilimumab–naïve melanoma comparing 10 mg/kg Q3W to 10 mg/kg Q2W) which shows a consistent response across all key efficacy parameters across 3 levels of exposure representing a 8.6 fold difference (7.5 fold difference in dose) - see Table 37 below.

Table 37: Cross-study comparison of key efficacy endpoints by dose level in KEYNOTE-001 Part D and KEYNOTE-006

	KEYNOTE-001 (Part D)		KEYNOTE-006	
	2 mg/kg Q3W	**10 mg/kg Q3W**	**10 mg/kg Q3W**	**10 mg/kg Q3W**
ORR (%)	33	35	33	34
PFS (median, mo)	5.5	4.2	4.1	5.5
6-month PFS rate (%)	50	41	46	47
OS (median)	not reached	not reached	not reached	not reached
12-month OS rate (%)	72	64	68	74

4.8 Subgroup analysis

KEYNOTE-006[18;23]

Subgroup analyses of PFS and OS

The study protocol specified that the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint would be estimated and plotted within each category of the following classification variables:

- Age category (≤65 vs. >65 years)
- Sex (female, male)
- Race (white, non-white)
- ECOG status (0 vs. 1)
- Line of therapy (first vs second)
- Prior treatment with a BRAF or MEK inhibitor (yes vs. no)
- BRAF mutation status
- Region (US, Ex-US)
- PD-L1 expression (high vs. low) (depending on assay availability)
- Human leukocyte antigen (HLA-A*0201) (positive vs. negative) (depending on availability of data)
- Prior immunotherapy such as interferon, peg-interferon, and IL-2 (yes vs. no)

The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above. Additionally, patients with high PD-L1 expression level were of special interest in this study.

Subgroup analyses were performed based on major demographic factors and potentially important prognostic factors for subjects with advanced melanoma. All analyses are based on efficacy outcomes in the ITT population, as determined by central (IRO) assessment per RECIST 1.1 criteria.

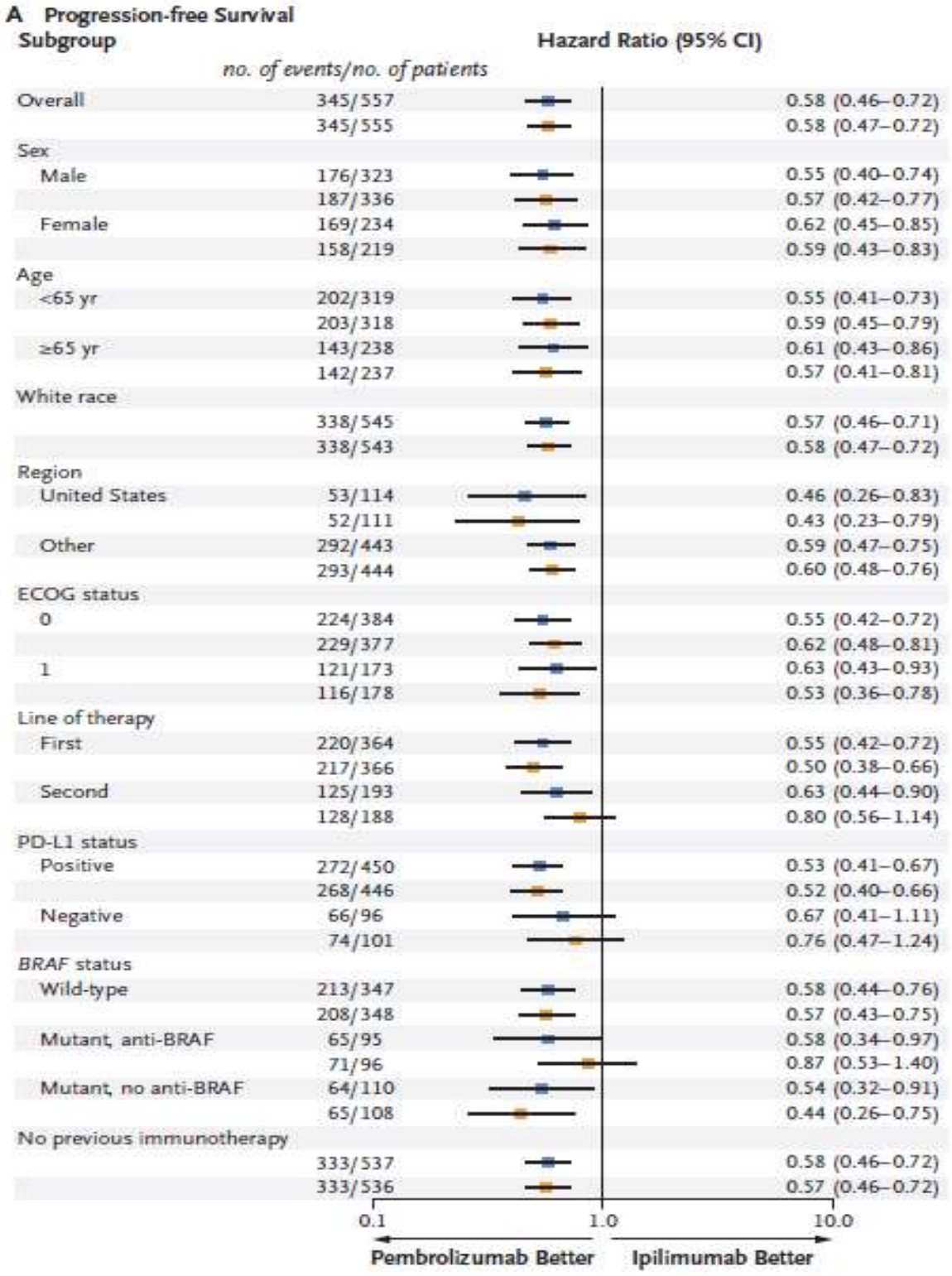
Figure 14 and
Figure 15 below summarises the HR and the corresponding 95% CI for PFS and OS respectively by key subgroups in the pembrolizumab 10 mg/kg Q2W arm and the 10 mg/kg Q3W arm versus the ipilimumab control arm, using a stratified Cox proportional model. Subgroup analyses for PFS is based on IA1, whereas subgroup analyses for OS is based on IA2.

The treatment effect on PFS was consistent in all subgroups in favouring the pembrolizumab dosing regimens over the ipilimumab arm, with CIs of all subgroups overlapping with the overall HR point estimate. The treatment effect on OS was consistent in all subgroups (with the exception of subjects with PD-L1 negative melanoma and subjects with baseline tumour size < median), in favouring the pembrolizumab dosing regimens over the ipilimumab arm, with CIs of all subgroups overlapping with the overall HR point estimate. For the 18% of subjects with PD-L1–negative tumours, the HRs were 0.91 and 1.02 for the pembrolizumab 10 mg/kg Q2W and Q3W arms, respectively, compared with ipilimumab. Of note, the sample sizes were small and the confidence intervals were wide. For subjects with baseline tumour size less than the median, the HR was 0.77 and 1.00 for the pembrolizumab 10 mg/kg Q2W and Q3W arms, respectively, compared with ipilimumab. In summary, the positive PFS and OS effect of pembrolizumab was overall consistent in all subgroups.

Subgroup analyses based on ORR for the pembrolizumab 10 mg/kg Q3W arm compared to ipilimumab and the pembrolizumab 10 mg/kg Q2W arm compared to ipilimumab, are in

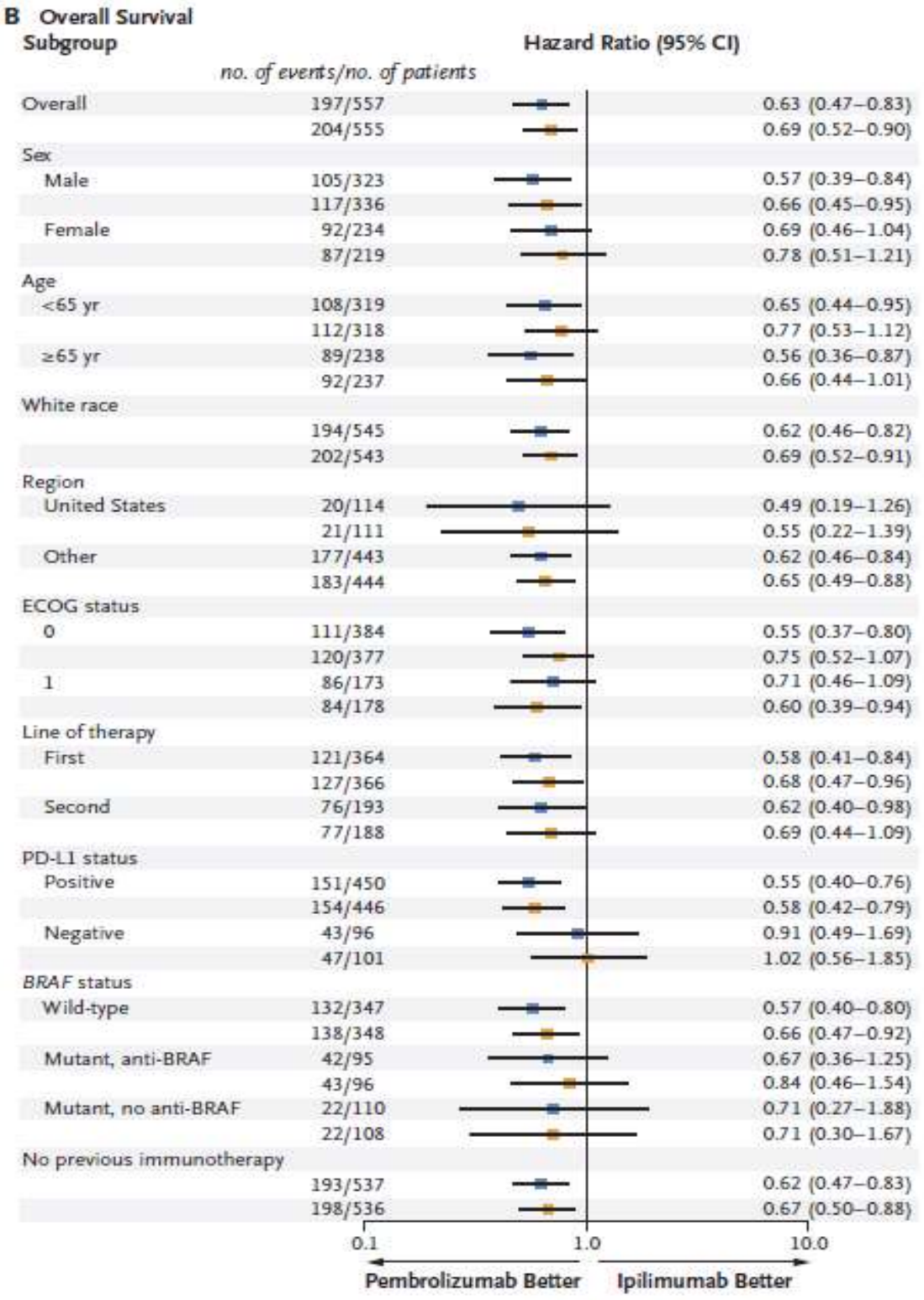
Figure 16 and Figure 17 respectively. The Forest plots display the difference in ORR (95% CIs) between treatment arms, calculated using Miettinen & Nurminen method. The ORR result is favourable for pembrolizumab compared to ipilimumab in all subgroups, except for those that received study treatment as second line therapy for pembrolizumab 10 mg/kg Q3W vs. ipilimumab; and those with an ECOG performance score of 1 for pembrolizumab 10 mg/kg Q2W vs. ipilimumab. The ORRs are comparable between pembrolizumab Q3W and ipilimumab in subjects who received study treatment as second line therapy; and between pembrolizumab Q2W and ipilimumab in those subjects with an ECOG 1 performance status.

Figure 14: KEYNOTE-006 - Pre-specified subgroup analysis of PFS, according to pembrolizumab regimen[18]



Shown are hazard ratios for PFS as of September 3, 2014, among patients receiving pembrolizumab every 2 weeks (blue squares) or every 3 weeks (orange squares) versus ipilimumab.
ECOG = Eastern Cooperative Oncology Group,
PD-L1= programmed cell death 1 ligand 1.

Figure 15: KEYNOTE-006 - Pre-specified subgroup analysis of OS, according to pembrolizumab regimen[18]



Shown are hazard ratios for OS as of March 3, 2015, among patients receiving pembrolizumab every 2 weeks (blue squares) or every 3 weeks (orange squares) versus ipilimumab.
ECOG = Eastern Cooperative Oncology Group,
PD-L1= programmed cell death 1 ligand 1

Figure 16: KEYNOTE-006 - Pembrolizumab 10 mg/kg Q3W versus Ipilimumab 3 mg/kg - Forest Plot of ORR by subgroup factors – Central (IRO) assessment per RECIST 1.1

		N/# Events	ORR Diff	95% CI
Overall		555/124	17.2	(9.5,25.6)
Gender				
	Male	336/92	22.3	(10.9,34.2)
	Female	219/32	7.8	(-1.7,23.6)
Age				
	< 65	318/59	21.4	(12.2,32.7)
	>= 65	237/65	11.7	(-0.2,25.9)
Race				
	White	543/122	17.1	(9.2,25.7)
Region				
	US	111/31	33.9	(12.6,54.7)
	Ex-US	444/93	14.6	(6.2,23.4)
Baseline ECOG Status				
	0	377/89	33.0	(11.0,53.0)
	1	178/35	11.7	(-0.9,26.1)
Baseline LDH				
	Normal	353/92	23.2	(7.8,37.1)
	Elevated	189/29	11.1	(3.2,22.8)
BRAF Mutation				
	Mutant	204/39	20.0	(8.4,34.8)
	Wild Type	351/85	12.9	(1.2,25.2)
Line of Therapy				
	First line	366/93	32.8	(20.9,45.0)
	Second line	188/31	-2.6	(-18.1,16.7)
PD-L1 Status				
	PD-L1 Positive	446/109	24.8	(16.6,33.0)
	PD-L1 Negative	101/15	5.9	(-3.4,14.0)
baseline Tumor Size Group				
	< Median	241/71	27.9	(13.8,42.9)
	>= Median	243/47	14.2	(2.2,25.8)

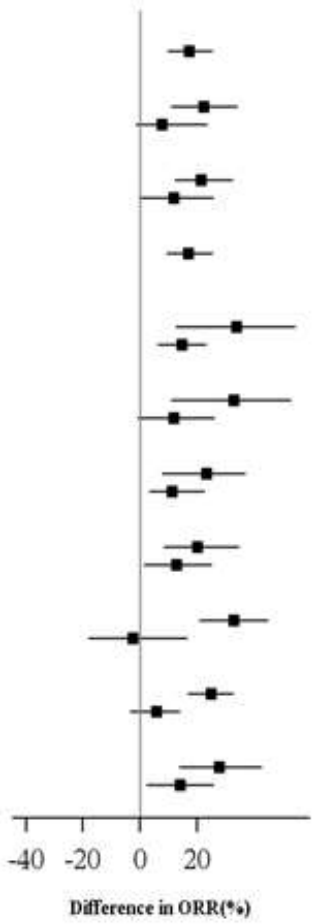
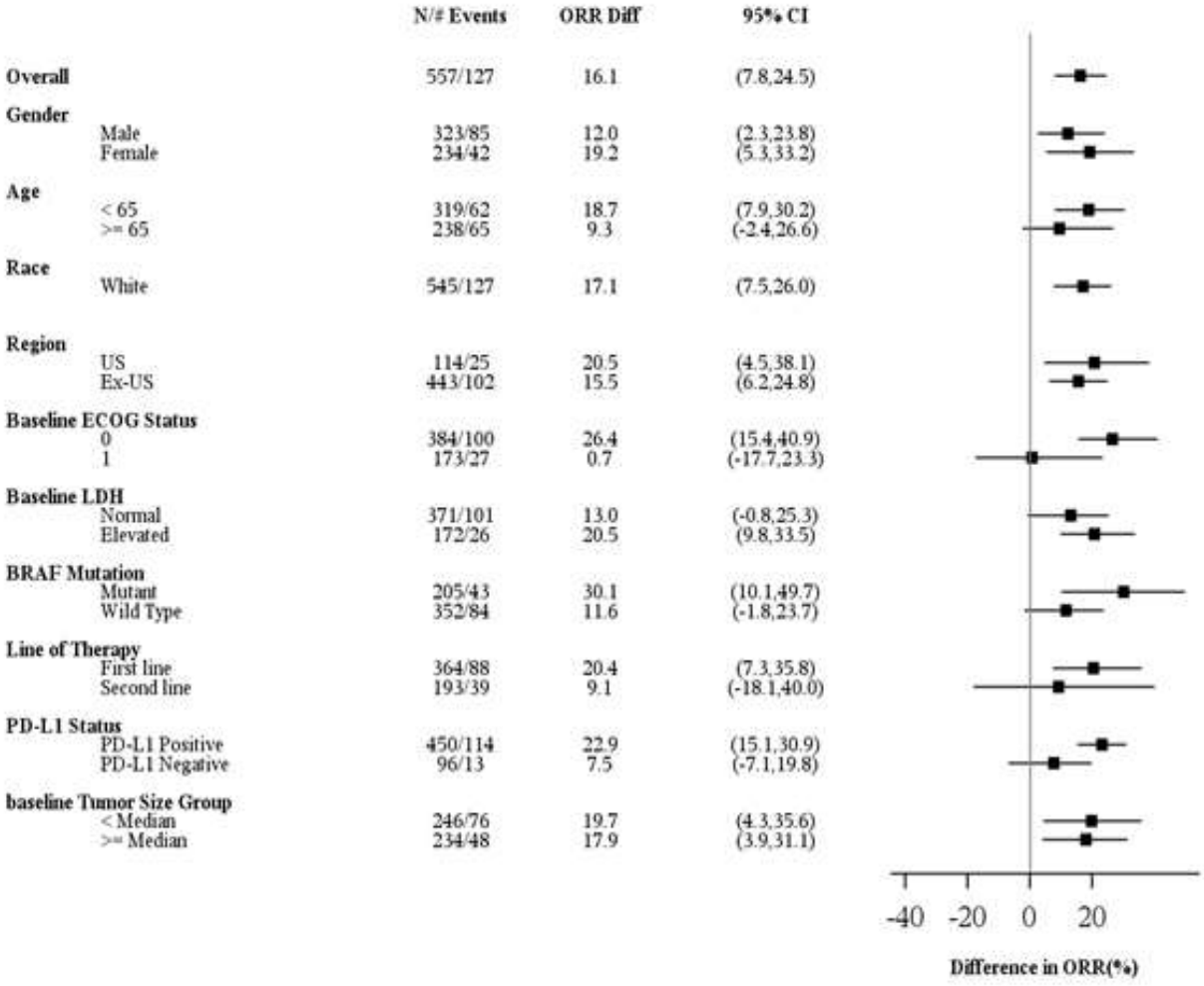


Figure 17: KEYNOTE-006 - Pembrolizumab 10 mg/kg Q2W versus Ipilimumab 3 mg/kg - Forest Plot of ORR by subgroup factors – Central (IRO) assessment per RECIST 1.1



Further details on efficacy sub-group analyses based on PD-L1 expression (a secondary endpoint of KEYNOTE-006) are presented in Appendix 6.

KEYNOTE-001 Part D[70]

Subgroup analyses were performed based on major demographic factors and potentially important prognostic factors for patients with advanced melanoma. These subgroups were not pre-specified, but were performed in post-hoc analyses to show consistency in ORR for major subgroups who might be treated with pembrolizumab in future clinical trials or in future clinical practice. All analyses were based on ORR as determined by central review (IRO) per RECIST 1.1[78] in the APaT population.

Further details are provided in Appendix 6.

4.9 Meta-analysis

There is only one randomised controlled trial for the intervention versus a relevant comparator (KEYNOTE-006). KEYNOTE-001 Part D did not include a comparator of relevance to the decision problem. A meta-analysis was not conducted as it was deemed inappropriate to pool pembrolizumab data from these two studies, given their different designs and differences in patient baseline characteristics between both studies (in particular ECOG status, previous lines of therapy, and elevated LDH (Table 38).

Table 38: Comparison of key baseline characteristics from KEYNOTE-006 and KEYNOTE-001 – Part D

	KEYNOTE-006			KEYNOTE-001 Part D	
	Pembrolizumab		Ipilimumab	Pembrolizumab	
	10 mg/kg Q2W	10 mg/kg Q3W		2 mg/kg Q3W	10 mg/kg Q3W
N	279	277	278	51	52
Male (%)	57.70%	62.80%	58.30%	62.70%	59.60%
Age median	61	63	62	60	60
Age range	18-89	22-89	18-88	35-80	26-78
ECOG 0 (%)	70.30%	68.20%	67.60%	80.40%	88.50%
ECOG 1 (%)	29.70%	31.80%	32.40%	19.60%	11.50%
M1c stage at entry (%)	64.20%	68.20%	63.70%	62.7%	80.8%
BRAFV600 mutation	35.10%	35.00%	38.50%	39.20%	30.8%
Brain metastasis	8.20%	9.70%	10.10%	2.00%	9.6%
Previous lines of tx					
0	65.60%	66.80%	65.10%	45.10%	55.8%
1	34.40%	32.90%	34.90%	33.3%	28.8%
Elevated LDH (%)	29.00%	35.40%	33%	41.2%	28.8%

4.10 Indirect and mixed treatment comparisons

The comparators of relevance to the decision problem are ipilimumab and dacarbazine, in addition to vemurafenib and dabrafenib (the latter two being relevant in the $BRAF^{V600}$ mutation positive population only).

4.10.1 Search strategy

Full details of the search strategy used to identify trials involving comparators of relevance to the decision problem are included in Appendix 7.

4.10.2 Details of treatments

The decision problem identifies ipilimumab, dacarbazine, vemurafenib and dabrafenib as relevant comparators to pembrolizumab in the population of interest (the latter two only being relevant in the BRAFT mutation positive sub-population).

4.10.3 Criteria used in trial selection

The inclusion and exclusion selection criteria, language restrictions and the study selection process are described in Table 39 below:

Table 39: Criteria used in the trial selection process

Criteria	Inclusion	Exclusion
Population	Patients with unresectable stage III or IV melanoma, naïve to treatment with ipilimumab	Patients with non-cutaneous melanoma (i.e. ocular or mucosal melanoma) and with unknown primary site
Interventions	The following treatments as monotherapy or as combination therapy:* • pembrolizumab • ipilimumab 3mg/kg • dacarbazine (DTIC) • vemurafenib • dabrafenib	Any other intervention
Comparisons	Any of the interventions listed above, other interventions that have been compared to at least two of the interventions above	Any other comparison
Outcomes	At least one of the two outcomes:** • Progression-free survival (PFS) • Overall survival (OS) • Overall response (OR)	Other efficacy and safety outcomes are considered for analysis, but each study must include at least one of those presented to the left
Study Design	Randomised controlled trials	Non-randomised clinical trials, prospective and retrospective observational studies, case studies
Language restrictions	Studies published in English language	Any other language

*DTIC – trade name for dacarbazine; *Relevant combination treatments needed to include at least 2 of the interventions listed; **Note: the scope of the review includes extraction of safety outcomes, but for selection of relevant studies the focus is on efficacy outcomes*

4.10.4 Summary of trials

Table 40: Summary of the trials

Trial	Treatment 1	Treatment 2	Treatment 3
Robert et al 2015 (KEYNOTE-006) (NCT01866319)[1;18;23;69]	Pembrolizumab 10 mg/kg Q2W	Pembrolizumab 10 mg/kg Q3W	Ipilimumab 3 mg/kg Q3W
Hauschild et al 2012 (BREAK-3) (NCT01227889)[30;81]	Dabrafenib 150 mg bid	DTIC 1000 mg/m^2 Q3W	
Chapman et al 2011/ McArthur et al 2014 (BRIM-3) (NCT01006980)[5;8;8;82]	Vemurafenib 960 mg bid	DTIC 1000 mg/m^2 Q3W	
Hersh et al 2011 (NCT00050102)[83;84]	Ipilimumab 3 mg/kg Q4W	DTIC 250 mg/m^2 5 days/3 weeks + Ipilimumab 3 mg/kg Q4W	
Robert et al 2011 (NCT00324155)[33;85]	DTIC 850 mg/m^2 Q3W+ Ipilimumab 10 mg/kg weeks 1, 4, 7, and 10	DTIC 850 mg/m^2 Q3W	
Hodi et al 2010 (NCT00094653)[86;87]	Ipilimumab 3mg/kg Q3W + gp100 Q3W	Ipilimumab 3mg/kg Q3W	gp100 Q3W

BREAK-3,[30;81] BRIM-3,[5;8;8;82] and Hersh et al 2011)[83;84] allowed for crossover. In BREAK-3,[30;81] patients were crossed over from the DTIC 1000 mg/m2 Q3W arm to the dabrafenib 150 mg bid arm if there was evidence of disease progression as determined by a masked independent review committee. BRIM-3[5;8;8;82] allowed patients to cross over from the DTIC 1000 mg/m2 Q3W to the vemurafenib 960 mg bid arm if recommended by the data safety monitoring board. Finally, Hersh et al 2011[83;84] allowed patients to crossover from the monotherapy arm (ipilimumab 3 mg/kg Q4W) to the combination therapy arm (DTIC 250 mg/m2 5 days/3 weeks + ipilimumab 3 mg/kg Q4W) following disease progression.

Full details on the treatment and design characteristics of the included trials are provided in Appendix 8 (Table 1)

4.10.5 Trials identified in search strategy

All trials selected as part of the systematic literature review were included in the network meta-analysis (NMA).

4.10.6 Rationale for choice of outcome measure chosen

The outcomes of interest for the NMA were PFS and OS. Although there have been advancements in treatments for melanoma, 5-year survival proportion averages less than

50%.[5;33;83;86] Current treatments are developed with the aim of increasing survival time. It is for this reason that OS was chosen as an outcome of interest. Since OS is not yet mature for pembrolizumab and OS is not only affected by the treatment under study but also subsequent treatment after disease progression, PFS was also considered an outcome of interest.[88]

4.10.7 Populations in the included trials

The populations of interest were first-line BRAF^{V600} wild type, second-line BRAF ^{V600} wild type, and first-line BRAF ^{V600} mutation positive. Given the available studies, no analysis is performed for second-line BRAF ^{V600} mutation positive patients. The competing interventions for first-line and second-line BRAF wild type were pembrolizumab, ipilimumab 3 mg/kg, and dacarbazine. For the first-line BRAF ^{V600} mutation positive population, pembrolizumab, ipilimumab 3 mg/kg, DTIC, and vemurafenib and dabrafenib were considered. For pembrolizumab, ipilimumab and DTIC, the assumption was made that BRAF ^{V600} mutation status is not an effect modifier and 'all comers' results as observed in the individual trials are applicable to both sub-populations and used as such. Depending on the available studies, NMA of the first-line and second-line populations were performed separately or simultaneously. With the latter approach, adjustment for differences among first-line and second-line patients were made by means of meta-regression analysis.

4.10.8 Apparent or potential differences in patient populations between the trials

Details regarding previous systemic treatment experience among patients of the included trials are provided in Appendix 8 (Table 2). Two trials, BRIM-3[5;8;8;82] and Robert et al 2011,[33;85] did not allow for any prior systemic treatment. BREAK-3[30;81] and Hersh et al 2011[83;84] allowed for previous use of immunotherapy, but not chemotherapy. Finally, KEYNOTE-006[1;18;23;69] and Hodi et al 2010[86;87] allowed for any type of previous systemic treatment.

The distributions of baseline patient characteristics within and between comparisons are presented in Figures 1-12 of Appendix 7. Characteristics such as age, proportion of males, proportion of patients that are white, proportion of patients with ECOG scores of 0 were similar across comparisons. Proportion of patients with an ECOG score of 0 was between 66% and 71% for all comparisons, with the exception of ipilimumab 3 mg/kg Q3W + gp100 Q3W versus ipilimumab 3 mg/kg Q3W versus gp100 Q3W, which reported between 52% and 58% of patients with an ECOG score of 0. This is in contrast to the proportion of patients with a baseline ECOG score of 1; Hodi et al 2010[86;87] (which compared ipilimumab 3 mg/kg Q3W + gp100 Q3W, ipilimumab 3 mg/kg Q3W and gp100 Q3W) reported more than 40% of patients in this category, whereas Robert et al 2011[33;85] (which compared dacarbazine 850 mg/m2 Q3W + ipilimumab 10 mg/kg weeks 1, 4, 7, and 10 and DTIC 850 mg/m2 Q3W), BRIM-3[5;8;8;82] (which compared vemurafenib 960 mg bid and DTIC 1000 mg/m2 Q3W), and KEYNOTE-006[1;18;23;69] (which compared pembrolizumab 10 mg/kg Q2W, pembrolizumab 10 mg/kg Q3W, and

ipilimumab 3 mg/kg Q3W) reported proportions of 32% and below. Proportion of patients with melanoma stage M0 was below 5% in all comparisons. More than half of the trials reported proportions of patients with melanoma stage M1a below 15%, the exception being Robert et al 2011[33;85] and Hersh et al 2011.[83;84] Hersh et al 2011[83;84] and Robert et al 2011[33;85] were also the only studies that reported greater than 20% of patients in melanoma stage M1b. As such, these two studies (and their respective comparisons) were the only studies that reported a proportion of patients in melanoma stage M1c below 60%. Proportion of patients with brain metastasis and proportion of patients with LDH level above the upper limit of normal was similar across comparisons. In two studies (BRIM-3[5;8;8;82] and BREAK-3[30;81]), each assessing BRAF inhibitors, all patients had a $BRAF^{V600}$ mutation, and in one study (KEYNOTE-006[1;18;23;69]), 35% of patients had any $BRAF^{V600}$ mutation.

4.10.9; 4.10.10; 4.10.11 Methods, outcomes, baseline characteristics, risk of bias

Full details can be found in Appendix 8 (Tables 3-7).

4.10.12 Methods of analysis and presentation of results

In Appendix 9, an overview of concepts and models for NMA are provided.

Feasibility assessment

In order to gauge the appropriateness of proceeding with an NMA[89] the feasibility assessment included: 1) an assessment of whether the RCT evidence for the interventions of interest formed one evidence network for each population and outcome of interest; and 2) an assessment of the distribution of study and patient characteristics that may have affected treatment effects across direct comparisons of the evidence networks. An overview of alternative network diagrams are presented for NMA when the competing interventions of interest are limited to pembrolizumab, ipilimumab, DTIC, vemurafenib and dabrafenib (See section 4.10.12 (Table 41) and Appendix 9, Figures 3-10)

Evaluation of consistency between direct and indirect comparisons

The currently available evidence base did not consist of closed loops defined by multiple trials. As such evaluation of consistency between direct and indirect estimates was not performed for the current project.

Network meta-analysis

Based on the findings of the feasibility assessment, the results of the RCTs that are part of one evidence network and deemed sufficiently similar were synthesized by means of NMAs by outcome of interest. Under the assumption of consistency, the NMA model relates the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of

each intervention compared to control. Based on these basic parameters, the relative treatment effects between each of the contrasts in the network were obtained.

Given the network structure assumed for the analysis, there may be systematic differences in effect-modifiers between trials. For evidence networks that include first-line trials, second-line trials, and trials with a mixed first-line/second-line population, a meta-regression model with a covariate related to the proportion of second-line patients was used when at least one direct comparison in the network provide between-study variation regarding proportion of 2L patients, i.e. scenarios 3a and 3b. Such an analysis provided estimates of relative treatment effects between competing interventions for first-line patients as well as second-line patients. Given the limited evidence base, the assumption was made that the impact of a covariate on relative treatment effects was the same for all interventions in the network, i.e. a NMA meta-regression model with one parameter per covariate.

Models, likelihood, priors

All analyses were performed in the Bayesian framework and involved a model with parameters, data and a likelihood distribution, and prior distributions. See Appendix 9 for further details.

Adjustment for crossover

For the analysis of OS, it is important to note that after disease progression with the control treatment, patients may crossover to the active treatment. As such, the relative treatment effect of the intervention of interest relative to a control may be underestimated for OS. In an attempt to minimize this potential bias, reported KM curves adjusted for crossover were used whenever available.

If KM curves were not reported for a crossover adjusted OS analysis, an estimate was made of the relative treatment effect for OS by a prediction based on the relative treatment effect for PFS according to Flaherty et al 2014.[90] Specifically the Kaplan-Meier PFS data for the OS analysis was adjusted to obtain time varying log HRs according to $\ln(hr_{OS})=0.6319*\ln(hr_{PFS}) - 0.0309$, applicable to each time point.

Software

The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the OpenBUGS software package.[91;92] A first series of iterations from the OpenBUGS sampler was discarded as 'burn-in', and the inferences were based on additional iterations using two chains. All analyses were performed using R version 3.0.3 (http://www.r-project.org/) and OpenBugs version 3.2.3 (OpenBUGS Project Management Group).

Key assumptions

The key assumptions used in the analysis are summarised as follows:

- Given the evidence available for pembrolizumab, an assumption was made that the efficacy of 10 mg Q3W is equivalent to the efficacy of 2 mg Q3W, the licensed dosing regimen.
- For treatments not specifically targeting BRAF, the results for the all-comers population was used for both BRAF wild type and $BRAF^{V600}$ mutation positive analyses assuming BRAF status is not a significant effect-modifier.
- Given the structure of the network and the interventions used to connect the different trials, the assumption was made that there are no systematic differences in treatment effect for these interventions. For example, if a trial comparing ipilimumab 3 mg with ipilimumab 3mg + DTIC is connected to a trial comparing ipilimumab 10 mg + DTIC with DTIC, the analyses assumed that ipilimumab 3 mg + DTIC and ipilimumab 10 mg + DTIC have similar efficacy.
- For the BRIM-3 trial (vemurafenib versus DTIC)[5;8;8;82] the reported KM OS curves reflect the ITT population with crossover that has occurred among patients in the DTIC arm. For the crossover adjusted analysis performed, no KM curves are available in the literature, but only reported HRs. The HR for OS obtained with the crossover adjusted analysis is similar to the HR for OS without such adjustment. Accordingly, the KM OS curves reported (without crossover adjustment) was assumed representative for an analysis where no crossover would have occurred.
- For the BREAK-3 trial (dabrafenib versus DTIC)[30;81] the available KM OS curves are affected by crossover. In the absence of a crossover adjusted analysis in the literature, an assumption was made that the log HR over time between dabrafenib and DTIC for PFS and OS is similar with respect to their shape parameters, and only differ regarding scale. Under this assumption we can use the meta-analysis of PFS-OS relationship by Flaherty et al 2014[90] to obtain time-varying log HRs as if crossover would not have occurred.
- Similarly, Hersh et al 2011[83;84] does not provide PFS curves, but can be obtained based on OS curves and use of the meta-analysis of PFS-OS relationship by Flaherty et al 2014[90] to obtain time-varying log HR for PFS. Note that Hersh et al 2011 had crossover limiting the value of this study for both OS and PFS estimates.

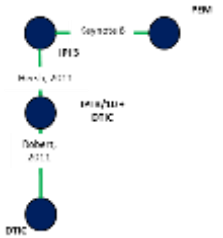
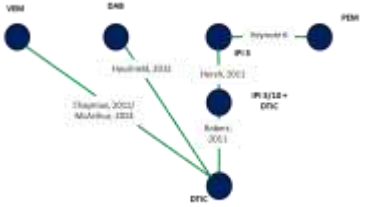
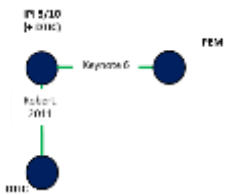
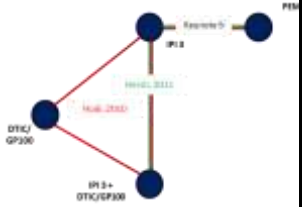
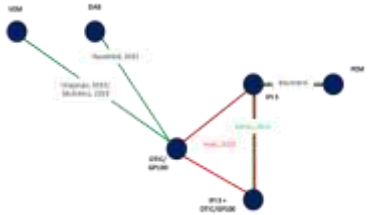
4.10.13 Programming language

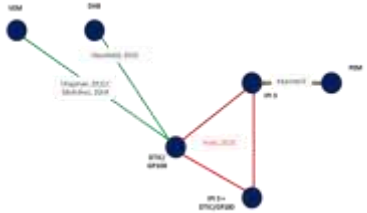
Programming language has been provided in Appendix 10

4.10.14; 4.10.15; 4.10.16 Results of analysis and results of statistical assessment of heterogeneity

Table 41 provides an overview of the different scenarios for the NMA of PFS and OS. Each of the different scenarios consists of a different network structure thereby making different assumptions regarding which interventions can be considered similar in order to connect different trials (see Appendix 9, Figures 3-10 for further details). Given each of the different networks, the main difference across trials is proportion of patients that are first-line and second-line and absence or presence of crossover from the control group to the intervention group of interest. In scenario 3a and 3b we attempted to adjust for between-trial differences in the proportion of patients with second-line treatment (KEYNOTE-006[18;23] first-line subgroup has 0%; KEYNOTE-006[18;23] second-line subgroup has 100%; Hersh 2011[83;84] has 45.8% second-line; Robert 2011[33;85] has 0% second-line; Hodi 2010[86;87] has 100% second-line; BREAK-3[30;81] has 26.8% second-line (prior immunotherapy); and BRIM-3[5;8;8;82] has 0% second-line).

Table 41: Overview of scenarios and related assumptions and limitations

Scenario	wild type population	BRAF^{V600} mutation positive population	1L/2L	Analysis of PFS / OS	Assumptions / limitations
1			1L	PFS OS	Ipilimumab 3 mg/kg + DTIC assumed similar as ipilimumab 10 mg/kg + DTIC Hersh et al 2011 had crossover affecting OS HRs Hersh et al 2011 had no PFS requiring use of OS data and relationship between HR PFS and HR OS based on Flaherty et al 2014 In Hersh et al 2011 patients were chemotherapy naïve but 45.8% had previous immune therapy BREAK-3 had crossover affecting OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty et al 2014 BREAK-3 patients were chemotherapy naïve but 26.8% had previous immune therapy BRIM-3 has crossover but HR with and without crossover adjustment was similar. As such reported OS KM curves without crossover adjustment were assumed to represent relative treatment effects without crossover.
2			1L	PFS OS	Ipilimumab 3 mg/kg assumed similar as ipilimumab 10 mg/kg + DTIC BREAK-3 had crossover affecting OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty et al 2014 In BREAK-3 patients were chemotherapy naïve but 26.8% had previous immune therapy BRIM-3 has crossover but HR with and without crossover adjustment was similar. As such reported OS KM curves without crossover adjustment were assumed to represent relative treatment effects without crossover.
3a			1L 2L (wild type only)	OS	Ipilimumab 3 mg/kg + DTIC assumed similar as ipilimumab 3 mg/kg + gp100 DTIC assumed similar as gp100 Hersh et al 2011 had crossover affecting OS HRs BREAK-3 had crossover affecting OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty et al 2014 BRIM-3 had crossover but HR with and without crossover adjustment was similar. As such reported OS KM curves without crossover adjustment were assumed to represent relative treatment effects without crossover. Covariate in model to adjust for between-trial differences in proportion 2L (i.e. proportion previous systemic treatment: Keynote 006 1L covariate=0; Keynote 006 1L covariate=1; Hodi 2010 covariate =1; Hersh et al 2011 covariate =0.458; BRIM-3 covariate = 0; BREAK-3 covariate =0.268) The relative difference in relative treatment effects between 1L and 2L is the same for all interventions relative to IPI 3. In other words, the covariate estimate is treatment independent.

Scenario	wild type population	BRAF^{V600} mutation positive population	1L/2L	Analysis of PFS / OS	Assumptions / limitations
3b			1L 2L	PFS OS	Ipilimumab 3 mg/kg + DTIC assumed similar as ipilimumab 3 mg/kg + gp100 DTIC assumed similar as gp100 BREAK-3 has crossover affecting OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty et al 2014 BRIM-3 has crossover but HR with and without crossover adjustment was similar. As such reported OS KM curves without crossover adjustment were assumed to represent relative treatment effects without crossover. Covariate in model to adjust for between-trial differences in proportion 2L (i.e. proportion previous systemic treatment: Keynote 006 1L covariate=0; Keynote 006 1L covariate=1; Hodi et al 2010 covariate =1; Hersh et al 2011 covariate =0.458; BRIM-3 covariate = 0; BREAK-3 covariate =0.268) The relative difference in relative treatment effects between 1L and 2L is the same for all interventions relative to ipilimumab 3 mg/kg. In other words, the covariate estimate is treatment independent.

DTIC – trade name for dacarbazine; HR – hazard ratio; OR – overall response; OS – overall survival; PFS – progression-free survival; KM – Kaplan-meier; 1L – first line; 2L – second line

The study specific KM curves for PFS and OS as obtained from the individual studies and extracted source data used for the NMA are presented in Appendix 11. The Weibull model was used to estimate relative treatment effects between interventions with the NMA. Given that the evidence base is characterised by one study for each direct comparison (within subgroups of first-line and second-line), it was not feasible to estimate the between-study heterogeneity parameter.

For each of the scenarios presented above in Table 41, tabulated results of the NMA are provided as follows:

- Results of NMA; first-line treatment,
    - OS: Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments (Table 42) and treatment effects as hazard ratio at different time points relative to ipilimumab (Table 43)
    - PFS: Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments (Table 44) and treatment effects as hazard ratio at different time points relative to ipilimumab (Table 45)
- Results of NMA; second-line treatment,

- OS: Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments (Table 46) and treatment effects as hazard ratio at different time points relative to ipilimumab (Table 47)
- PFS: Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments (Table 48) and treatment effects as hazard ratio at different time points relative to ipilimumab (Table 49)

OS: First-line population

Table 42: Results of NMA; first-line treatment, OS: Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments

		Hazard Ratio with PEM relative to other treatments*											
		Scenario 1			Scenario 2			Scenario 3a			Scenario 3b		
Reference* treatment	Time point (months)	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high
IPI**	6	0.59	0.42	0.83	0.59	0.42	0.84	0.57	0.42	0.79	0.59	0.41	0.84
	12	0.59	0.38	0.92	0.59	0.38	0.93	0.59	0.40	0.87	0.61	0.39	0.93
	18	0.59	0.34	1.04	0.60	0.34	1.05	0.60	0.38	0.97	0.62	0.37	1.04
DTIC**	6	0.65	0.25	1.92	0.45	0.30	0.67	0.58	0.37	0.88	0.54	0.30	0.91
	12	0.55	0.28	1.00	0.43	0.26	0.71	0.49	0.30	0.79	0.44	0.24	0.81
	18	0.51	0.23	1.09	0.42	0.23	0.79	0.45	0.24	0.80	0.40	0.20	0.81
VEM***	6	0.82	0.41	1.70	0.63	0.39	0.99	0.80	0.49	1.28	0.75	0.40	1.34
	12	0.48	0.23	0.92	0.38	0.21	0.67	0.43	0.24	0.75	0.39	0.20	0.74
	18	0.35	0.14	0.78	0.28	0.14	0.58	0.30	0.15	0.59	0.26	0.12	0.57
DAB***	6	1.06	0.46	2.45	0.80	0.43	1.51	1.05	0.53	1.95	0.96	0.46	1.93
	12	0.77	0.27	2.01	0.62	0.25	1.54	0.71	0.28	1.69	0.63	0.23	1.67
	18	0.64	0.18	2.07	0.53	0.17	1.64	0.57	0.18	1.66	0.49	0.15	1.59

*The hazard ratios are for the comparison of pembrolizumab in the column versus other treatments in the rows
**Applicable to wild type and BRAFmu+ populations
***Applicable to BRAFmu+ population

Table 43: Results of NMA; first-line treatment, OS: Treatment effects as hazard ratio at different time points relative to ipilimumab

		Hazard Ratio relative to IPI*											
		Scenario 1			Scenario 2			Scenario 3a			Scenario 3b		
Treatment*	Time point (months)	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high
DTIC**	6	1.01	0.52	1.78	1.32	1.08	1.63	0.99	0.64	1.60	1.08	0.57	2.19
	12	1.08	0.71	1.84	1.38	1.14	1.70	1.21	0.77	1.92	1.36	0.70	2.77
	18	1.13	0.71	2.07	1.41	1.12	1.81	1.37	0.83	2.21	1.55	0.77	3.25
PEM**	6	0.59	0.42	0.83	0.59	0.42	0.84	0.57	0.42	0.79	0.59	0.41	0.84
	12	0.59	0.38	0.92	0.59	0.38	0.93	0.59	0.40	0.87	0.61	0.39	0.93
	18	0.59	0.34	1.04	0.60	0.34	1.05	0.60	0.38	0.97	0.62	0.37	1.04
VEM***	6	0.72	0.37	1.32	0.95	0.70	1.29	0.71	0.43	1.20	0.77	0.40	1.66
	12	1.23	0.76	2.25	1.57	1.12	2.22	1.38	0.81	2.34	1.55	0.78	3.30
	18	1.69	0.96	3.48	2.11	1.38	3.24	2.03	1.11	3.65	2.32	1.09	5.14
DAB***	6	0.56	0.25	1.19	0.74	0.44	1.24	0.55	0.30	1.07	0.61	0.28	1.46
	12	0.76	0.32	1.97	0.97	0.45	2.12	0.84	0.35	2.01	0.96	0.35	2.76
	18	0.92	0.32	2.91	1.14	0.43	2.98	1.07	0.38	3.10	1.26	0.38	4.22

*The hazard ratios are for the comparison of the treatment in the row versus ipilimumab in the column
**Applicable to wild type and BRAFmu+ populations
***Applicable to BRAFmu+ population

PFS: First-line population

Table 44: Results of NMA; first-line treatment, PFS: Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments

		Hazard Ratio with PEM relative to other treatments*								
		Scenario 1			Scenario 2			Scenario 3b		
Reference* treatment	Time point (months)	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high
IPI**	3	0.51	0.39	0.66	0.50	0.38	0.66	0.50	0.38	0.65
	6	0.46	0.32	0.64	0.45	0.32	0.64	0.45	0.33	0.62
	12	0.41	0.24	0.71	0.41	0.23	0.71	0.41	0.26	0.64
DTIC**	3	0.70	0.21	2.58	0.43	0.30	0.60	0.54	0.33	0.82
	6	0.50	0.17	1.46	0.34	0.22	0.50	0.36	0.21	0.59
	12	0.36	0.12	1.00	0.27	0.14	0.49	0.24	0.12	0.48
VEM***	3	1.88	0.54	7.09	1.15	0.77	1.72	1.46	0.84	2.35
	6	0.93	0.32	2.78	0.63	0.39	0.97	0.67	0.37	1.14
	12	0.46	0.14	1.36	0.34	0.17	0.68	0.31	0.15	0.65
DAB***	3	2.27	0.60	9.28	1.40	0.80	2.42	1.76	0.88	3.26
	6	1.11	0.29	4.04	0.75	0.33	1.71	0.80	0.32	1.92
	12	0.55	0.09	2.71	0.40	0.11	1.49	0.36	0.09	1.44

*The hazard ratios are for the comparison of pembrolizumab in the column versus other treatments in the rows
**Applicable to wild type and BRAFmu+ populations
***Applicable to BRAFmu+ population

Table 45: Results of NMA; first-line treatment, PFS: Treatment effects as hazard ratio at different time points relative to ipilimumab

		Hazard Ratio relative to IPI*								
		Scenario 1			Scenario 2			Scenario 3b		
Treatment*	Time point (months)	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high
DTIC**	3	0.72	0.20	2.41	1.18	0.95	1.47	0.91	0.56	1.70
	6	0.91	0.33	2.47	1.34	1.09	1.65	1.23	0.75	2.22
	12	1.13	0.47	2.93	1.53	1.13	2.08	1.67	0.93	3.15
PEM**	3	0.51	0.39	0.66	0.50	0.38	0.66	0.50	0.38	0.65
	6	0.46	0.32	0.64	0.45	0.32	0.64	0.45	0.33	0.62
	12	0.41	0.24	0.71	0.41	0.23	0.71	0.41	0.26	0.64
VEM***	3	0.27	0.07	0.91	0.44	0.33	0.59	0.34	0.20	0.66
	6	0.49	0.17	1.37	0.72	0.54	0.98	0.66	0.38	1.27
	12	0.88	0.34	2.50	1.19	0.77	1.85	1.32	0.67	2.68
DAB***	3	0.22	0.06	0.81	0.36	0.22	0.59	0.28	0.15	0.59
	6	0.41	0.12	1.49	0.60	0.29	1.28	0.55	0.23	1.41
	12	0.74	0.17	3.96	1.01	0.31	3.34	1.12	0.30	4.28

*The hazard ratios are for the comparison of the treatment in the row versus ipilimumab in the column
**Applicable to wild type and BRAFmu+ populations
***Applicable to BRAFmu+ population

OS: Second-line population

Table 46: Results of NMA; second-line treatment, OS: Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments

		Hazard Ratio with PEM relative to other treatments*					
		Scenario 3a			Scenario 3b		
Reference* treatment	Time point (months)	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high
IPI**	6	0.84	0.55	1.26	0.80	0.52	1.22
	12	0.87	0.54	1.40	0.83	0.51	1.36
	18	0.89	0.51	1.55	0.84	0.48	1.51
DTIC**	6	0.57	0.35	0.93	0.53	0.32	0.88
	12	0.48	0.29	0.84	0.44	0.25	0.80
	18	0.44	0.24	0.84	0.40	0.20	0.78

*The hazard ratios are for the comparison of pembrolizumab in the column versus other treatments in the rows
**Applicable to wild type population

Table 47: Results of NMA; second-line treatment, OS: Treatment effects as hazard ratio at different time points relative to ipilimumab

		Hazard Ratio relative to IPI*					
		Scenario 3a			Scenario 3b		
Treatment*	Time point (months)	estimate	95%CrI low	95%CrI high	estimate	95%CrI low	95%CrI high
DTIC**	6	1.47	1.13	1.91	1.50	1.15	1.96
	12	1.79	1.34	2.37	1.86	1.40	2.50
	18	2.02	1.42	2.80	2.11	1.49	3.03
PEM**	6	0.84	0.55	1.26	0.80	0.52	1.22
	12	0.87	0.54	1.40	0.83	0.51	1.36
	18	0.89	0.51	1.55	0.84	0.48	1.51

*The hazard ratios are for the comparison of the treatment in the row versus ipilimumab in the column
**Applicable to wild type population

PFS: Second-line population

Table 48: Results of NMA; second-line treatment, PFS: Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments

		Hazard Ratio with PEM relative to other treatments*		
		Scenario 3b		
Reference* treatment	Time point (months)	estimate	95%CrI low	95%CrI high
IPI**	3	0.81	0.58	1.15
	6	0.74	0.48	1.12
	12	0.67	0.38	1.16
DTIC**	3	0.51	0.33	0.80
	6	0.34	0.21	0.56
	12	0.23	0.12	0.45

*The hazard ratios are for the comparison of pembrolizumab in the column versus other treatments in the rows
**Applicable to wild type population

Table 49: Results of NMA; second-line treatment, PFS: Treatment effects as hazard ratio at different time points relative to ipilimumab

		Hazard Ratio relative to IPI*		
		Scenario 3b		
Treatment*	Time point (months)	estimate	95%CrI low	95%CrI high
DTIC**	3	1.59	1.22	2.06
	6	2.15	1.62	2.83
	12	2.91	1.94	4.36
PEM**	3	0.81	0.58	1.15
	6	0.74	0.48	1.12
	12	0.67	0.38	1.16

*The hazard ratios are for the comparison of the treatment in the row versus ipilimumab in the column
**Applicable to wild type population

Appendix 12 (Figures 1 – 51) additionally presents the NMA results for PFS and OS with estimates for treatment effects of each intervention relative to ipilimumab in terms of scale and shape parameters. Based on these parameter estimates, plots of the HR as a function of time of each intervention relative to ipilimumab are presented. Furthermore, the HR of pembrolizumab relative to the competing interventions are presented as well. PFS and OS curves using the ipilimumab control group in KEYNOTE-006 act as an anchor to transform relative treatment effects into modeled PFS and OS over time.

Summary of results:

With regards to the wild-type population, competing interventions for pembrolizumab are ipilimumab 3 mg/kg and DTIC. The efficacy and safety of pembrolizumab 10 mg/kg Q3W relative to ipilimumab 3 mg/kg is provided by the KEYNOTE-006 trial which demonstrated prolonged PFS and OS and less high-grade toxicity with pembrolizumab in patients with advanced melanoma. The licensed dose for pembrolizumab will be 2 mg/kg Q3W, but in the absence of trial data among ipilimumab naïve patients, the relative efficacy of pembrolizumab in the KEYNOTE-006 trial is assumed applicable and was used in the NMA to obtain relative effect estimates versus DTIC. Several NMAs were performed and each of the different scenarios consists of a different network structure thereby making different assumptions regarding which interventions can be considered similar in order to connect different trials (See Table 41 and Appendix 9). The different scenario analyses all indicate that pembrolizumab results in a greater PFS and OS than ipilimumab and DTIC in an ipilimumab naïve population without a history of systemic treatment for advanced melanoma (i.e. first-line). For the second-line population the results indicate that pembrolizumab is at least as efficacious as ipilimumab 3 mg/kg.

The results obtained with the different scenario analyses did not affect the estimate of pembrolizumab relative to ipilimumab 3 mg/kg, but only the estimates of ipilimumab 3 mg/kg relative to DTIC and therefore pembrolizumab relative to DTIC. Of the four different scenarios, scenarios 2 and 3b are most likely the most trustworthy because they did not include the trial by Hersh et al 2011,[83] which did not provide PFS data, had crossover between treatment groups (unlike other trials used for the wild type population and could not be adjusted for), and included patients with a history of immunotherapy despite being chemotherapy naïve. The main assumption of scenario 2 is that ipilimumab 3 mg/kg has a similar efficacy as ipilimumab 10 mg/kg in combination with DTIC. The main assumption with scenario 3b is that the efficacy of ipilimumab 3 mg/kg relative to gp100 among second-line patients is applicable to a comparison of ipilimumab 3 mg/kg versus DTIC after adjustment

for the study level treatment effect modifier proportion of first-line/second-line estimated based on KEYNOTE-006 data.

With regards to the $BRAF^{V600}$ mutation positive population with advanced melanoma, first-line treatment is typically either dabrafenib or vemurafenib. However, a subset of patients may be treated first with ipilimumab given the short duration of response with the BRAF inhibitors. Hence, for the $BRAF^{V600}$ mutation positive population, dabrafenib and vemurafenib were considered the primary competing interventions of pembrolizumab, but ipilimumab 3 mg/kg and DTIC were considered as well. These two latter interventions were needed in the NMA to provide a "path" from pembrolizumab to dabrafenib and vemurafenib. For the NMA of competing interventions applicable to the $BRAF^{V600}$ mutation positive population the pembrolizumab and ipilimumab study findings were assumed applicable to a $BRAF^{V600}$ mutation positive population (i.e. BRAF status is not an effect modifier for these interventions). Accordingly the relative treatment effects for pembrolizumab relative to ipilimumab 3 mg/kg and DTIC as obtained with the NMA assumed applicable for the $BRAF^{V600}$ mutation positive population are the same as for the wild type population. As suggested by this NMA, pembrolizumab seems to have a similar efficacy as vemurafenib and dabrafenib. However, extrapolating the trend of relative treatment effects over time, pembrolizumab may have an advantage after 1 year of follow-up (see Appendix 12).

NMA for survival outcomes based on the constant HR rely on the proportional hazards assumption, which is implausible if the hazard functions of competing interventions cross. As an alternative to the constant HR, which is a univariate treatment effect measure, a multivariate treatment effect measure that describes how the relative treatment effect (e.g. HR) develops over time can also be used. Different competing survival models were used for the NMA, but only the Weibull model which assumes that treatment has an effect on both scale and shape seemed a good compromise between model fit to the data and plausible extrapolation of relative treatment effects beyond the trial follow-periods available.

In summary, based on the currently available RCT evidence, pembrolizumab demonstrates greater PFS and OS relative to ipilimumab 3 mg/kg and DTIC for the treatment of advanced melanoma among patients naïve to ipilimumab and not previously treated with systemic treatment. Pembrolizumab seems to have at least comparable efficacy as vemurafenib and dabrafenib among $BRAF^{V600}$ mutation positive patients without a history of systemic treatment, and based on extrapolation, pembrolizumab may have an advantage after 1 year of follow-up.

4.10.17 Justification for the choice of random or fixed effects model

In general, the assumptions of random effects models are more plausible than fixed effect models. However, given that the evidence base that is characterized by one study for each direct comparison (within subgroups of first-line and second-line) it was not feasible to estimate the between-study heterogeneity parameter, and thus we used a fixed effects model.

4.10.18; 4.10.19 Relevance of trials and heterogeneity between results of pairwise comparisons

Please refer to Table 41; and see section 4.10.17 above

4.11 Non-randomised and non-controlled evidence

4.11.1 Non-randomised evidence

Non-randomised evidence of relevance to the decision problem is provided in Table 50 below.

Table 50: List of relevant non-randomised and non-controlled evidence

Study number (acronym)	Objective	Population	Intervention	Comparator	Primary study reference	Justification for inclusion
KEYNOTE-001 Part B1[74]	To evaluate the safety profile of pembrolizumab (formerly called lambrolizumab) assess tumour response every 12 weeks	Patients with measurable metastatic or locally advanced unresectable melanoma, both those who had received prior therapy with ipilimumab and those who had not.	Pembrolizumab 2 mg/kg Q3W	• Pembrolizumab 10 mg/kg Q2W • Pembrolizumab 10 mg/kg Q3W	Hamid O et al (2013) Safety and tumor responses with lambrolizumab (Anti-PD-1) in melanoma *NEJM* 369:2 134-144[74]	Additional published evidence on the efficacy and safety of pembrolizumab

4.11.2 Trials excluded from further discussion

Not applicable

4.11.3 Summary of the methodology of the studies in a table

The methodology of KEYNOTE-001 Part B1 is summarised in Table 51 below.

Table 51: Summary of trial methodology

Trial number (acronym)	KEYNOTE-001 – Part B1[74]
Location	The full KEYNOTE-001 study was conducted across the following countries: Australia, Canada, Denmark, France, Germany, Israel, Italy, Norway, South Korea, Spain, Taiwan, UK, USA.
Trial design	Phase 1 expansion study
Eligibility criteria for participants	• 18 years of age or older • measurable metastatic or locally advanced unresectable melanoma • adequate performance status and organ function (according to criteria listed in the protocol). The cohorts of patients who had not received prior treatment with ipilimumab were restricted to: • patients who had received no more than two prior regimens of systemic therapy. The cohorts of patients who had received prior therapy with ipilimumab included only: • patients who had full resolution of ipilimumab-related adverse events and no history of severe immune-related adverse events associated with ipilimumab therapy. • patients were allowed to enter the trial 6 weeks after the last dose of ipilimumab was administered. Patients with previously treated brain metastases were required to undergo baseline imaging by means of computed tomographic scanning or magnetic resonance imaging and to have had no evidence of central nervous system progression for 8 weeks. Major exclusion criteria were: • a melanoma of ocular origin • prior therapy with a PD-1 or PD-L1 blocking agent • current systemic immunosuppressive therapy • active infections or autoimmune diseases
Settings and locations where the data were collected	The study was run in specialists oncology departments. Patients received treatment as day care patients.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=) and comparator(s) (n=)** **Permitted and disallowed concomitant medication**	Pembrolizumab 2 mg/kg Q3W (n=22) Pembrolizumab 10 mg/kg Q2W (n=57) Pembrolizumab 10 mg/kg Q3W (n=56) Current systemic immunosuppressive therapy was disallowed
Primary outcomes (including scoring methods and timings of assessments)	Evaluation of safety profile of pembrolizumab.
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	Preliminary analysis of the anti-tumour activity of pembrolizumab, both in patients who had received prior treatment with ipilimumab and in those who had not.
Pre-planned subgroups	Not Applicable

4.11.4 Statistical analysis of the non-randomised evidence

Of the 135 patients with melanoma included in Part B1 of KEYNOTE-001,[74] 117 had radiographically measurable disease as assessed by means of central radiologic review and were included in the efficacy analysis of responses according to central review.

All other efficacy analyses (analysis of response based on investigator assessment, PFS and OS) were based on data from all 135 patients.[74] Patients who had received a first dose of study medication by 06 September 2012 were included in the analysis. Efficacy and safety data that were available as of 01 February 2013 were included in all the analyses. Efficacy analysis included two end points: overall responses based on investigator-reported data assessed according to irRC[77] (n=135) which was considered the primary measure for assessment of tumour response; and overall responses based on independent central, blinded radiologic review assessed according to RECIST 1.1[78] (n = 117) as supportive analyses.

ORR was defined as the number of patients with a complete or partial response divided by the total number of patients who had measurable disease at baseline and received at least one treatment dose. The overall response rate and exact two-sided 95% confidence interval were calculated.

4.11.5 Participant flow in KEYNOTE-001 Part B1

Initially patients were enrolled in a cohort that received pembrolizumab at a dose of 10 mg/kg Q2W. Subsequently, additional patients were enrolled in concurrent (non-randomised) cohorts that received pembrolizumab 10 mg/kg or 2 mg/kg Q3W. Distinction was made between patients who had received (48 patients) and those who had not received (87 patients) prior treatment with ipilimumab in order to provide preliminary data on the safety and antitumor activity of pembrolizumab on the basis of prior or no prior treatment with ipilimumab. All patients treated at the 2 mg/kg dose had not received prior treatment with ipilimumab.

The baseline characteristics of the participants who received the 2 mg/kg dose are provided in Table 52 below.

Table 52: Characteristics of participants in the Part B1 across treatment groups[74]

Characteristics	10 mg/kg Q2W		10 mg/kg Q3W		2 mg/kg Q3W	Total n = 135
	No prior ipilimumab (n=41)	Prior ipilimumab (n=16)	No prior ipilimumab (n=24)	Prior ipilimumab (n=32)	No prior ipilimumab (n=22)	
Sex; n(%)						
• Male	23 (56)	9 (56)	16 (67)	17 (53)	14 (64)	79 (59)
• Female	18 (44)	7 (44)	8 (33)	15 (47)	8 (36)	56 (41)
Age (yr)						
• ***Mean***	60.4	59.4	67	57.3	58.6	60.4
• ***Range***	25–94	29–87	37–87	32–77	30–79	25–94
Race*; n(%)						
• Asian	0	0	2 (8)	0	0	2 (1)
• White	41 (100)	16 (100)	22 (92)	32 (100)	22 (100)	133 (99)
ECOG PS†; n(%)						
• Unknown	1 (2)	0	0	0	0	1 (1)
• 0	32 (78)	13 (81)	18 (75)	21 (66)	13 (59)	97 (72)
• 1	8 (20)	3 (19)	6 (25)	11 (34)	9 (41)	37 (27)
BRAF status; n(%)						
• Mutant	13 (32)	1 (6)	1 (4)	5 (16)	6 (27)	26 (19)
• Wild Type	23 (56)	14 (88)	21 (88)	21 (66)	14 (64)	93 (69)
• Unknown	5 (12)	1 (6)	2 (8)	6 (19)	2 (9)	16 (12)
Brain metastasis; n(%)						
• Yes	3 (7)	3 (19)	0	4 (12)	2 (9)	12 (9)
• No	38 (93)	13 (81)	24 (100)	28 (88)	20 (91)	123 (91)
LDH Level; n(%)						
• Normal	23 (56)	11 (69)	16 (67)	17 (53)	13 (59)	80 (59)
• Elevated‡	13 (32)	5 (31)	6 (25)	7 (22)	5 (23)	36 (27)
• Unknown	5 (12)	0	2 (8)	8 (25)	4 (18)	19 (14)
M staging of extent of metastasis; n(%)						
• MX	0	0	0	1 (3)	0	1 (1)

• M0	7 (17)	2 (12)	2 (8)	3 (9)	1 (5)	15 (11)
• M1a	1 (2)	3 (19)	6 (25)	3 (9)	1 (5)	14 (10)
• M1b	11 (27)	3 (19)	7 (29)	5 (16)	2 (9)	28 (21)
• M1c	20 (49)	8 (50)	9 (38)	18 (56)	18 (82)	73 (54)
• Unknown	2 (5)	0	0	2 (6)	0	4 (3)
Previous therapy[§]; n(%)						
• No prior systemic therapy	16 (39)	0	12 (50)	0	14 (64)	42 (31)
• Immunotherapy, excluding ipilimumab	11 (27)	4 (25)	5 (21)	10 (31)	4 (18)	34 (25)
• Chemotherapy	11 (27)	8 (50)	9 (38)	14 (44)	5 (23)	47 (35)
• BRAF	4 (10)	0	1 (4)	4 (12)	1 (5)	10 (7)

** Race was self-reported.*
† An Eastern Cooperative Oncology Group (ECOG) performance status of 0 indicates that the patient is fully active, 1 that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, and 2 that the patient is ambulatory and capable of all self-care but unable to carry out any work activities.
‡ An elevated level was considered to be a level higher than the upper limit of the normal range.
§ This category included treatments for advanced disease. The numbers may add up to more than 100% since a patient may have received more than one type of oncologic therapy.

The baseline characteristics of the patients included in Part B1 were similar across all the treatment groups (Table 1). Overall >50% of the patients had visceral metastases (stage M1c), approximately 25% had an elevated LDH level, and close to 9% had a history of brain metastases. These characteristics are all recognized as poor prognostic factors in patients with advanced melanoma.

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

Risk of bias of KEYNOTE-001 – Part B1[74] has been assessed using the Newcastle-Ottawa Scale,[93] which was identified in a previous systematic review[94] as one of the two most useful tools for assessing the methodological quality of non-randomised studies of interventions. Assessment has been conducted at a study level.

Information from KEYNOTE-001 Part B1 is not being used in any data synthesis.

A summary of the quality appraisal of Part B1 –KEYNOTE-001 is provided in Table 53 below, with full details provided in Appendix 13.

Table 53: Quality assessment of KEYNOTE-001 – Part B1

Criteria	Star assignment
Selection: 1) Representativeness of the exposed cohort 2) Selection of the non exposed cohort 3) Ascertainment of exposure 4) Demonstration that outcome of interest was not present at start of study	 One star One star One star One star
Comparability 1) Comparability of cohorts on the basis of the design or analysis	Two stars
Outcome 1) Assessment of outcome 2) Was follow-up long enough for outcomes to occur 3) Adequacy of follow up of cohorts	 One star One star One star

Clinical effectiveness results of the relevant non-randomised and non-controlled evidence (As of analysis date: March 2013)[74]

Response to therapy was evaluated using the following two criteria:

- Investigator-assessed per immune-related response criteria (irRC):[77] designed to analyse the response to immunotherapy agent
- Independent, central radiologic review per RECIST 1.1:[78] used routinely to assess responses to cytotoxic agents for cancer.

The ORR during receipt of therapy, across all doses, was 37% based on investigator assessment per irRC criteria.[77] The confirmed response rate across all doses, as assessed by central review according to RECIST 1.1,[78] was 38% (44 of 117 patients). There were an additional 8 unconfirmed responses, 6 of which were in patients who had not yet undergone confirmatory scanning at the time of the data cut-off. Since then, 1 of these patients has been confirmed as having an objective response.

The RR, including confirmed and unconfirmed responses, across all doses was 44% (44 confirmed and 8 unconfirmed). The confirmed response rate, as assessed by central review according to RECIST 1.1[78] 1.1, ranged from 25% in the 2 mg/kg Q3W cohort to 52% in the 10 mg/kg Q2W cohort.

77% of the patients had a reduction in the tumour burden during the study, including 8 patients who were confirmed by central review as having stable disease for longer than 24 weeks (Figure 18). Responses did not vary according to prior exposure to ipilimumab (Table 54 and Figure 18).

Time to response and treatment duration in the 52 patients who had an objective response (confirmed or unconfirmed) on the basis of central radiologic review according to RECIST 1.1[78] are shown in Figure 19. Most responses were seen at the time the first imaging was performed (12 weeks). An additional 17 patients who had stable disease at an early assessment showed durable objective response with continued treatment, with 1 patient achieving a partial response according to RECIST 1.1[78] after 48 weeks of treatment. Median duration of response had not been reached at the time of the analysis, at a median follow-up time of 11 months.

81% of those patients who had a response were continuing to receive study treatment at the time of the analysis (March 2013). Of the 52 patients with a response, 5 discontinued treatment owing to disease progression, and 5 discontinued treatment for other reasons (most commonly adverse events).

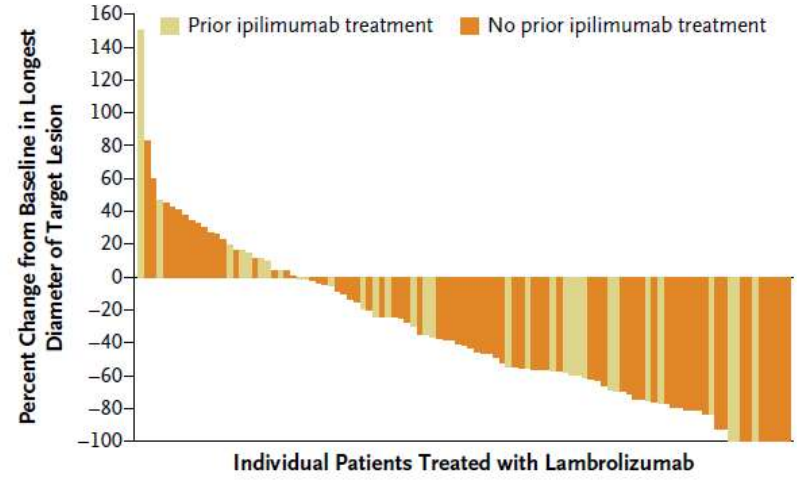
Median progression-free survival among the 135 patients, as estimated with the use of a KM analysis, was > 7 months. The estimated median overall survival had not been reached.

Table 54: KEYNOTE 001 Part B1: ORR according to dosing regimen and status with respect to prior therapy with ipilimumab, as assessed according to RECIST1.1 and irRC[74]

Pembrolizumab Regimen and Ipilimumab Status	RECIST			Immune-Related Response (irRC)		
	No. of Patients	Confirmed and Unconfirmed Objective Response	Confirmed Objective Response	Duration of Response †	No. of Patients	Confirmed Objective Response
		no. (% [95% CI])				no. (% [95% CI])
10 mg/kg Q2W						
• **No prior ipilimumab**	39	21 (54 [37–70])	19 (49 [32–65])‡	1.9–10.8	41	23 (56 [40–72])
• **Prior ipilimumab**	13	8 (62 [32–86])	8 (62 [32–86])§	2.8–8.3	16	9 (56 [30–80])
• **Total**	52	29 (56 [41–69])	27 (52 [38–66	1.9–10.8	57	32 (56 [42–69])
10 mg/kg Q3W						
• **No prior ipilimumab**	19	7 (37 [16–62])	5 (26 [9–51])	2.6–5.6	24	8 (33 [16–55])
• **Prior ipilimumab**	26	9 (35 [17–56])	7 (27 [12–48])	2.8–8.3	32	7 (22 [9–40])
• **Total**	45	16 (36 [22–51])	12 (27 [15–42])	2.6–8.3	56	15 (27 [16–40])
2 mg/kg Q3W, no prior Ipilimumab	20	7 (35 [15–59])	5 (25 [9–49])¶	2.1–5.5	22	3 (14 [3–35])
Total‖	117	52 (44 [35–54])**	44 (38 [25–44])	1.9–10.8	135	50 (37 [29–45])

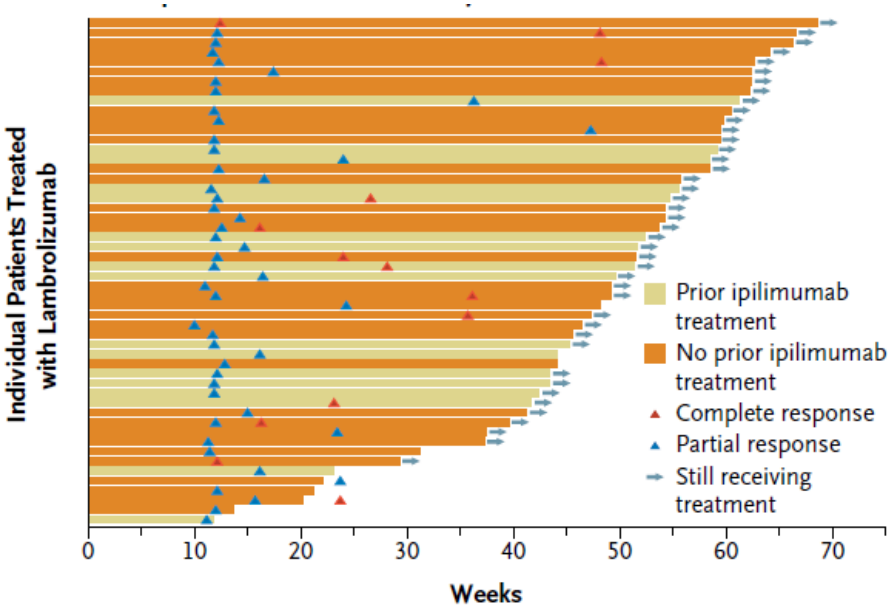
† Duration of response was defined as the time from the first response to the time of documented progression or, in the case of censored data, the most recent tumour assessment. All the lower and upper ranges listed are for censored data and refer to the time from the first response to the most recent tumour assessment, except for the lower range in the group with no prior ipilimumab, as well as the total cohort, receiving 10 mg/kg Q3W; these two lower ranges refer to the time from first response to the time of documented progression. Only confirmed responses were included in the calculation of duration of response.
‡ Three of these patients had a complete response.
§ Two of these patients had a complete response.
¶ One of these patients had a complete response.
‖ The confirmed response rate, according to RECIST, version 1.1, was 38% (95% CI, 23 to 55) among patients who had received prior ipilimumab treatment and 37% (95% CI, 26 to 49) among patients who had not received prior ipilimumab treatment.
*** Six patients with initial responses were awaiting confirmation of the response at the time of the data cut-off for this report. One response has since been confirmed, but since it was confirmed after the data cut-off for the presented analysis, the data on overall response rate have not been modified.*

Figure 18: Anti-tumour activity of pembrolizumab – Best Objective Response[74]



The above waterfall plot depicts best objective response according to prior treatment with ipilimumab, measured as the maximum change from baseline in the sum of the longest diameter of each target lesion. A total of 10 of 103 patients with radiographically measurable disease at baseline and at least one evaluation after treatment had a 100% reduction in target lesions.

Figure 19: Time to response and duration of study treatment[74]



The above figure shows the time to response and the duration of study treatment. A total of 42 of the 52 patients who had a response were still receiving the study treatment at the time of the current analysis. Of the 10 patients who discontinued therapy, 5 discontinued owing to toxic effects, and 2 of these patients showed improvement in their response after discontinuation.

4.12 Adverse reactions

4.12.2 Adverse reactions reported in RCTs listed in section 4.2

KEYNOTE-006: Adverse reactions

As per the results presented in section 4.7, the write up in this section focuses on the findings in the pembrolizumab 10 mg/kg Q3W arm versus ipilimumab, as the Q3W dosing schedule is likely to be the licensed dosing schedule of pembrolizumab.

For completeness, results are presented for both pembrolizumab 10 mg/kg study arms (Q3W and Q2W) in the tables and figures included in this section.[23]

The All Patients as Treated (APaT) population was used for the analysis of safety data in this study. Safety and tolerability were assessed by clinical and statistical review of AEs and laboratory value AEs reported during the treatment period up to the data cut-off for IA1 (03 Sep 2014).

AE summaries, counts, listings, and tables include events from the first dose to 30 days after the last dose of study treatment. Serious AE (SAE) counts and listing tables include events from the first dose to 90 days after last dose to account for the extended safety follow up period for SAEs. In the AE summary tables, all AEs, including SAEs, are reported up to 30 days after the last dose of study drug. Therefore, the incidence of SAEs in AE summary tables differs slightly from the incidence of SAEs in later sections, where SAE tables by system organ class (SOC) include SAEs captured up to 90 days after the last dose of study treatment. For AEs of special interest (AEOSI), summaries, counts, listings, and tables include non-serious AEs (NSAEs) from the first dose to 30 days after the last dose and SAEs from the first dose to 90 days after last dose.

Drug exposure in KEYNOTE-006 is summarised in Table 55 below. In the control arm, the mean number of doses of ipilimumab was 3.3 and the median number was 4. Ipilimumab treatment was administered over a mean of approximately 51 days (range 1 to 92 days) from the first to the last dose. Ipilimumab was planned to be given for up to 4 doses unless subjects had disease progression, intolerable toxicity or other discontinuation criteria, and the results show that exposure to ipilimumab was generally as planned. For pembrolizumab 10 mg/kg Q3W, mean exposure was 151 days (10 mg/kg Q3W arm, range 1-332 days). Subjects in both pembrolizumab arms had a mean duration on study treatment three times longer than subjects exposed to ipilimumab.

Table 55: KEYNOTE-006 - Summary of drug exposure (APaT population)

	Ipilimumab	Pembrolizumab 10 mg/kg Q3W	Pembrolizumab 10 mg/kg Q2W
	N=256	N=277	N=278
Study Days On-Therapy (days)			
• **Mean**	50.94	163.88	163.93
• **Median**	63.00	168.00	183.00
• **SD**	27.64	90.75	90.73
• **Range**	1.00 to 331.00*	1.00 to 332.00	1.00 to 336.00
Number of Administrations			
• **Mean**	3.29	8.00	12.00
• **Median**	4.00	9.00	13.00
• **SD**	0.99	4.26	5.89
• **Range**	1.00 to 4.00	1.00 to 16.00	1.00 to 20.00

** Data entry error identified after database lock: one subject (360969) whose last dose start date was 09-12-2013 but the last dose end date was entered incorrectly as 09-12-2014, i.e. this patient is the one with duration of 331 days (using 03SEP2014 cut-off date). This error was identified during IA1 CSR preparation and the site was queried and corrected*

The approximately one-third shorter treatment duration for ipilimumab subjects versus pembrolizumab subjects potentially confounds the interpretation of aggregated summary tables. To show weighted comparisons that adjust for differences in time on treatment, the following three analyses have been performed (see Appendix 14):

- AEs by time periods (i.e. a summary for each of three separate treatment time intervals: weeks 0-6; weeks 7-12 and weeks 13-18).
- Display and analysis of overall AEs (i.e. overall AEs by drug exposure (events/person year)
- Display and analysis of overall grade 3-5 AEs (i.e. time to first event to facilitate a direct comparison of the initial onset of toxicity for pembrolizumab versus ipilimumab)

These separate analyses show that ipilimumab toxicities tended to occur at a higher rate per unit time when a subject was receiving treatment; the AEs also occurred sooner in the ipilimumab treatment arm than in the pembrolizumab arms.

Table 56 presents the AE summary by treatment arm. In comparison to ipilimumab, pembrolizumab showed a comparable frequency of AEs, drug-related AEs, and Grade 3-5 AEs regardless of causality. Drug-related Grade 3-5 AEs were numerically higher in the ipilimumab arm compared to both pembrolizumab arms (19.9% compared to 10.1% in the pembrolizumab 10 mg/kg Q3W arm).

SAEs and drug-related SAEs were also more frequently reported in the ipilimumab arm compared to the pembrolizumab arms (30.1% for ipilimumab vs 24.9% for pembrolizumab 10 mg/kg Q3W when considering SAEs and 17.6% for ipilimumab vs 6.5% for pembrolizumab 10 mg/kg Q3W when considering drug-related SAEs). There was one drug-related death in the

ipilimumab arm, and no drug-related deaths in the pembrolizumab 10 mg/kg Q3W arm (one drug-related death is listed against the pembrolizumab 10 mg/kg Q2W arm, but the investigator changed the assessment of causality from related to unrelated after the database lock for the current analysis of KEYNOTE-006).[23] Discontinuations due to an AE were more frequent in patients on the ipilimumab arm compared to the pembrolizumab arms, as were discontinuations due to drug-related AEs. Most categories of AEs were similar between the two pembrolizumab treatment arms (Table 56).

Overall, these data show that pembrolizumab was generally well-tolerated and had numerically fewer drug-related Grade 3-5 AEs, fewer SAEs and drug-related SAEs, and fewer AEs leading to treatment discontinuation compared to ipilimumab.

Table 56: KEYNOTE-006- AE summary (APaT population)

	Ipilimumab		Pembrolizumab 10 mg/kg Q3W		Pembrolizumab 10 mg/kg Q2W	
	n	(%)	n	(%)	N	(%)
Subjects in population	256		277		278	
with one or more adverse events	239	(93.4)	264	(95.3)	275	(98.9)
with no adverse event	17	(6.6)	13	(4.7)	3	(1.1)
with drug-related† adverse events	187	(73.0)	202	(72.9)	221	(79.5)
with toxicity grade 3-5 adverse events	94	(36.7)	92	(33.2)	105	(37.8)
with toxicity grade 3-5 drug-related adverse events	51	(19.9)	28	(10.1)	37	(13.3)
with serious adverse events	77	(30.1)	69	(24.9)	71	(25.5)
with serious drug-related adverse events	45	(17.6)	18	(6.5)	31	(11.2)
who died	3	(1.2)	5	(1.8)	7	(2.5)
who died due to a drug-related adverse event	1	(0.4)	0	(0.0)	1*	(0.4)*
discontinued‡ due to an adverse event	34	(13.3)	30	(10.8)	20	(7.2)
discontinued due to a drug-related adverse event	24	(9.4)	19	(6.9)	11	(4.0)
discontinued due to a serious adverse event	25	(9.8)	23	(8.3)	18	(6.5)
discontinued due to a serious drug-related adverse event	19	(7.4)	12	(4.3)	9	(3.2)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA preferred terms 'Malignant neoplasm progression' and 'Neoplasm progression' not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
** one drug-related death is listed against the pembrolizumab 10 mg/kg Q2W arm, but note that the investigator changed the assessment of causality from related to unrelated after the database lock for the current analysis of KEYNOTE-006).*

It should be noted that these data represent the cumulative incidence of AEs, and do not account for a longer period of observation for AEs on the pembrolizumab treatment arms. In KEYNOTE-006, patients on the ipilimumab arm were followed during ipilimumab treatment and after completing ipilimumab treatment with planned every 3 week visits until disease progression or other discontinuation criteria were met, and then went into long term survival follow-up. Patients on the pembrolizumab arms were followed every 2 or 3 weeks until disease progression or other discontinuation criteria were met, and then went into long term follow-up. However, because patients on the ipilimumab arm had a higher rate of and earlier disease progression (as shown by the PFS curves – see Figure 8), patients on the pembrolizumab treatment arms generally had longer exposure and follow-up time for the collection of AEs. As such, the simple cumulative incidence of AEs may favour the ipilimumab arm in some categories of AEs.

- *Grade 3-5 AEs*

The time to onset of the first grade 3-5 AE (regardless of attribution), was longer in the pembrolizumab arms. Table 57 shows that grade 3-5 AEs occurred earlier in the course of treatment with ipilimumab compared with pembrolizumab.

Table 57: KEYNOTE-006 - Time to onset of first AE of Grade 3, 4, or 5 severity, regardless of attribution to study treatment (APaT population)[18]

	Ipilimumab N = 256	Pembrolizumab 10 mg/kg Q3W N = 277	Pembrolizumab 10 mg/kg Q2W N = 278
Patients with a grade 3, 4, or 5 event —no. (%)	94 (36.7)	92 (33.2)	105 (37.8)
Time to onset of first grade 3, 4, or 5 event —			days
Median (range)	39.5 (4-94)	64.0 (4-283)	59.0 (4-357)
Mean (SD)	42.4 (24.3)	88.0 (75.6)	86.6 (72.9)
Comparison of pembrolizumab vs ipilimumab —HR (95% CI)	—	0.52*** (0.38-0.72)	0.59*** (0.43-0.80)

****P<0.001.*
Abbreviations: CI, confidence interval; HR, hazard ratio; Q2W, every 2 weeks; Q3W, every 3 weeks; SD, standard deviation

- *Treatment-related AEs*

AEs considered by the investigator to be "possibly," "probably," or "definitely" related to study medication are combined into the category of treatment-related AEs (Table 58). The most common treatment-related AEs of any grade occurring in the pembrolizumab Q3W arm were fatigue (19.1%), diarrhoea (14.4%), rash (13.4%), and pruritus (14.1%). All events were of grade 3 to 4 severity in fewer than 1% of patients, with the exception of diarrhoea (which occurred in 1.1% of patients in the pembrolizumab Q3W arm. In the ipilimumab arm, the most frequent AEs were pruritus (25.4%), diarrhoea (22.7%), fatigue (15.2%), and rash (14.5%). These AEs were of grade 3 to 5 severity in less than 1% of patients, with the exception of diarrhoea (3.1%) and fatigue (1.2%).

Table 58: KEYNOTE-006 – AEs attributed to study treatment by the Investigator that occurred in ≥1% of patients in any treatment group (APaT population)[18]

	Ipilimumab N = 256		Pembrolizumab 10 mg/kg Q3W N = 277		Pembrolizumab 10 mg/kg Q2W N = 278	
	Any Grade no. (%)	Grade 3-5 no. (%)	Any Grade no. (%)	Grade 3-5 no. (%)	Any Grade no. (%)	Grade 3-5 no. (%)
Fatigue	39 (15.2)	3 (1.2)	53 (19.1)	1 (0.4)	58 (20.9)	0 (0.0)
Diarrhoea	58 (22.7)	8 (3.1)	40 (14.4)	3 (1.1)	47 (16.9)	7 (2.5)
Rash	37 (14.5)	2 (0.8)	37 (13.4)	0 (0.0)	41 (14.7)	0 (0.0)
Pruritus	65 (25.4)	1 (0.4)	39 (14.1)	0 (0.0)	40 (14.4)	0 (0.0)
Asthenia	16 (6.3)	2 (0.8)	31 (11.2)	0 (0.0)	32 (11.5)	1 (0.4)
Nausea	22 (8.6)	1 (0.4)	31 (11.2)	1 (0.4)	28 (10.1)	0 (0.0)
Arthralgia	13 (5.1)	2 (0.8)	32 (11.6)	1 (0.4)	26 (9.4)	0 (0.0)
Hypothyroidism	2 (0.8)	0 (0.0)	21 (7.6)	0 (0.0)	25 (9.0)	1 (0.4)
Vitiligo	4 (1.6)	0 (0.0)	31 (11.2)	0 (0.0)	25 (9.0)	0 (0.0)
Dry mouth	1 (0.4)	0 (0.0)	11 (4.0)	0 (0.0)	20 (7.2)	0 (0.0)
Myalgia	5 (2.0)	1 (0.4)	6 (2.2)	0 (0.0)	19 (6.8)	1 (0.4)
Decreased appetite	20 (7.8)	0 (0.0)	18 (6.5)	0 (0.0)	17 (6.1)	0 (0.0)
Hyperthyroidism	6 (2.3)	1 (0.4)	7 (2.5)	0 (0.0)	17 (6.1)	0 (0.0)
Aspartate aminotransferase increased	6 (2.3)	2 (0.8)	6 (2.2)	1 (0.4)	14 (5.0)	0 (0.0)
Alanine aminotransferase increased	9 (3.5)	2 (0.8)	4 (1.4)	1 (0.4)	12 (4.3)	0 (0.0)
Pyrexia	6 (2.3)	0 (0.0)	3 (1.1)	0 (0.0)	11 (4.0)	0 (0.0)
Abdominal pain	15 (5.9)	0 (0.0)	5 (1.8)	0 (0.0)	10 (3.6)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	12 (4.3)	0 (0.0)	10 (3.6)	0 (0.0)
Dysgeusia	3 (1.2)	0 (0.0)	5 (1.8)	0 (0.0)	10 (3.6)	0 (0.0)
Rash maculopapular	7 (2.7)	1 (0.4)	6 (2.2)	1 (0.4)	10 (3.6)	0 (0.0)
Vomiting	14 (5.5)	0 (0.0)	5 (1.8)	0 (0.0)	10 (3.6)	1 (0.4)

Headache	9 (3.5)	0 (0.0)	6 (2.2)	0 (0.0)	9 (3.2)	0 (0.0)
Dizziness	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	8 (2.9)	0 (0.0)
Erythema	5 (2.0)	0 (0.0)	3 (1.1)	0 (0.0)	8 (2.9)	0 (0.0)
Back pain	0 (0.0)	0 (0.0)	5 (1.8)	0 (0.0)	7 (2.5)	0 (0.0)
Constipation	5 (2.0)	0 (0.0)	5 (1.8)	0 (0.0)	7 (2.5)	0 (0.0)
Blood bilirubin increased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	6 (2.2)	0 (0.0)
Dry skin	3 (1.2)	0 (0.0)	8 (2.9)	0 (0.0)	6 (2.2)	0 (0.0)
Hypocalcemia	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	6 (2.2)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	6 (2.2)	0 (0.0)
Pain in extremity	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)	6 (2.2)	1 (0.4)
Arthritis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	5 (1.8)	0 (0.0)
Blood lactate dehydrogenase increased	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.8)	1 (0.4)
Skin hypopigmentation	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	5 (1.8)	0 (0.0)
Abdominal pain upper	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	4 (1.4)	0 (0.0)
Alopecia	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	4 (1.4)	0 (0.0)
Blood creatinine increased	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	4 (1.4)	0 (0.0)
Colitis	19 (7.4)	16 (6.3)	8 (2.9)	5 (1.8)	4 (1.4)	4 (1.4)
Conjunctivitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)
Dyspepsia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)
Dyspnoea	3 (1.2)	1 (0.4)	8 (2.9)	1 (0.4)	4 (1.4)	0 (0.0)
Eczema	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	4 (1.4)	0 (0.0)
Hair colour changes	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	4 (1.4)	0 (0.0)
Muscle spasms	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	4 (1.4)	0 (0.0)
Rash pruritic	4 (1.6)	0 (0.0)	3 (1.1)	0 (0.0)	4 (1.4)	0 (0.0)
Anaemia	1 (0.4)	1 (0.4)	6 (2.2)	0 (0.0)	3 (1.1)	2 (0.7)
Blood thyroid stimulating hormone decreased	2 (0.8)	1 (0.4)	3 (1.1)	0 (0.0)	3 (1.1)	0 (0.0)
Bone pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)
Chills	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)
Dermatitis	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)
Flushing	2 (0.8)	0 (0.0)	3 (1.1)	0 (0.0)	3 (1.1)	0 (0.0)
Hot flush	1 (0.4)	0 (0.0)	2 (0.7)	0 (0.0)	3 (1.1)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	3 (1.1)	2 (0.7)
Memory impairment	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)
Musculoskeletal stiffness	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	3 (1.1)	0 (0.0)
Neutrophil count decreased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)
Oropharyngeal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)
Papule	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	3 (1.1)	0 (0.0)
Peripheral edema	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)
Rash erythematous	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)
Weight decreased	5 (2.0)	1 (0.4)	3 (1.1)	0 (0.0)	3 (1.1)	0 (0.0)
Blood alkaline phosphatase increased	4 (1.6)	0 (0.0)	3 (1.1)	0 (0.0)	2 (0.7)	0 (0.0)

Blood thyroid stimulating hormone increased	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	2 (0.7)	0 (0.0)
Hypersensitivity	2 (0.8)	0 (0.0)	3 (1.1)	0 (0.0)	2 (0.7)	0 (0.0)
Hypomagnesemia	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	2 (0.7)	0 (0.0)
Influenza-like illness	4 (1.6)	1 (0.4)	6 (2.2)	0 (0.0)	2 (0.7)	0 (0.0)
Lethargy	3 (1.2)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.7)	0 (0.0)
Flatulence	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Hypertriglyceridemia	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)
Mucosal inflammation	3 (1.2)	0 (0.0)	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)
Skin lesion	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)
Soft feces	3 (1.2)	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)
Vision blurred	3 (1.2)	0 (0.0)	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)
Eosinophilia	2 (0.8)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Frequent bowel movements	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatocellular injury	3 (1.2)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypophysitis	4 (1.6)	2 (0.8)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Paresthesia	3 (1.2)	1 (0.4)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Rash papular	3 (1.2)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)

- *AEs with potential immune etiology*

An immune-related AE (irAE) is defined as an AE of unknown etiology, which is consistent with an immune phenomenon and is temporally associated with drug exposure. The analysis of AEs of special interest (AEOSI) was the primary method of assessing immune related AEs for this study and was based on a compiled list of preferred AE terms (developed by the study sponsor and based on ongoing monitoring of the pembrolizumab safety profile during the development program) potentially associated with an immune etiology.

The AEOSI are presented regardless of investigator assessed causality and generally include all AE grades (with the exception of severe skin reactions). In an attempt to capture all informative data, the list of terms is intentionally broad; consequently, some reported terms may not have an obvious immune mechanism. The list of terms is updated periodically based on emerging pembrolizumab safety data.

An overview of the number and percentage of subjects by study arm with any AEOSI in the APaT population is provided in Table 59 below. Overall, 109 of 555 (19.6%) of pembrolizumab treated subjects and 47 of 256 (18.4%) ipilimumab treated subjects were reported to have any AEOSI at the time of this analysis. Most AEOSIs were Grade 1-2 in severity and, despite the longer duration of exposure and observation for AEs, relatively fewer subjects in the pembrolizumab arm experienced high-grade (Grade 3 or 4) AEOSIs compared to subjects in

the ipilimumab arm (5.4% of subjects in the pembrolizumab arm versus 11.7% of subjects in the ipilimumab arm, respectively). In addition, a lower percentage of subjects in the pembrolizumab arm discontinued due to an AEOSI compared to the ipilimumab arm (2.7% versus 5.5% in the pembrolizumab and ipilimumab arms, respectively), and fewer pembrolizumab-treated subjects were discontinued due to AEOSIs that were considered SAEs compared to ipilimumab treated subjects (2.5% of subjects versus 5.1% of subjects in the pembrolizumab and ipilimumab arms, respectively). Results are presented for the pembrolizumab arms combined, as careful examination of AEOSIs by individual pembrolizumab treatment arms showed no evidence that a Q2W versus a Q3W dosing schedule made a difference in AEOSI frequency. No fatal AEOSIs occurred in any arm as of the data cut-off date (03 Sep 2014). Thus, while the cumulative frequency of all AEOSIs was numerically higher in the pembrolizumab arm compared to the ipilimumab arm, the frequency of high-grade AEOSIs, serious AEOSIs, and AEOSIs leading to discontinuation was approximately 2-fold higher for ipilimumab-treated subjects versus pembrolizumab-treated subjects.

Table 59: KEYNOTE-006 AE summary - AEOSI - (Pembrolizumab treatment groups combined) - APaT Population

	Ipilimumab 3mg/kg Q3W		Pembrolizumab combined	
	n	(%)	n	(%)
Subjects in population	256		555	
with one or more adverse events	47	(18.4)	109	(19.6)
with no adverse event	209	(81.6)	446	(80.4)
with drug-related[†] adverse events	43	(16.8)	94	(16.9)
with toxicity grade 3-5 adverse events	30	(11.7)	30	(5.4)
with toxicity grade 3-5 drug-related adverse events	29	(11.3)	24	(4.3)
with serious adverse events	27	(10.5)	28	(5.0)
with serious drug-related adverse events	26	(10.2)	25	(4.5)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	14	(5.5)	15	(2.7)
discontinued due to a drug-related adverse event	13	(5.1)	15	(2.7)
discontinued due to a serious adverse event	13	(5.1)	14	(2.5)
discontinued due to a serious drug-related adverse event	12	(4.7)	14	(2.5)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
AEs were followed 30 days after last dose of study
AEs of special interest per ECI guidance excluding Infusion Reactions
(Database cut-off date: 03SEP2014)

Further details on AEs of special interest, as pre-defined in the protocol based on likely autoimmune or immune-related mechanism, are provided below. Those most frequently observed with pembrolizumab 10 mg/kg Q3W were hypothyroidism (8.7%) and hyperthyroidism (3.2%) (Table 60).[18] The grade 3 - 4 events that were reported >1% of pembrolizumab 10 mg/kg Q3W treated patients were colitis (2.5%) and hepatitis (1.8%). In the ipilimumab group, the most common AEs of special interest was colitis (8.2% of patients). Grade 3 - 4 events that were reported in > 1% of ipilimumab-treated patients were colitis (7.0%) and inflammation of the pituitary gland (i.e., hypophysitis) (1.6%). Hypothyroidism and hyperthyroidism were more frequent in the pembrolizumab groups, whereas colitis and hypophysitis were more frequent in the ipilimumab group.[18]

Table 60: KEYNOTE-006 - AEs in the APaT population*[18]

	Ipilimumab (N = 256)		Pembrolizumab 10 mg/kg Q3W (N = 277)		Pembrolizumab 10 mg/kg Q2W (N = 278)	
Adverse Event	Any Grade	Grade 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (%)					
Related to treatment*						
• **Any**	187 (73.0)	51 (19.9)	202 (72.9)	28 (10.1)	221 (79.5)	37 (13.3)
• **Occurring in ≥10% of patients in any study group**						
○ **Fatigue**	39 (15.2)	3 (1.2)	53 (19.1)	1 (0.4)	58 (20.9)	0
○ **Diarrhoea**	58 (22.7)	8 (3.1)	40 (14.4)	3 (1.1)	47 (16.9)	7 (2.5)
○ **Rash**	37 (14.5)	2 (0.8)	37 (13.4)	0	41 (14.7)	0
○ **Pruritus**	65 (25.4	1 (0.4)	39 (14.1)	0	40 (14.4) 0	40 (14.4) 0
○ **Asthenia**	16 (6.3)	12 (0.8)	31 (11.2)	0	32 (11.5)	1 (0.4)
○ **Nausea**	22 (8.6)	1 (0.4)	31 (11.2)	1 (0.4)	28 (10.1)	0
○ **Arthralgia**	13 (5.1)	2 (0.8)	32 (11.6)	1 (0.4)	26 (9.4)	0
○ **Vitiligo**	4 (1.6)	0	31 (11.2)	0	25 (9.0)	0
Adverse event of special interest†						
○ **Hypothyroidism**	5 (2.0)	0	24 (8.7)	0	28 (10.1)	1 (0.4)
○ **Hyperthyroidism**	6 (2.3)	1 (0.4)	9 (3.2)	0	18 (6.5)	0
○ **Colitis**	21 (8.2)	18 (7.0)	10 (3.6)	7 (2.5)	5 (1.8)	4 (1.4)
○ **Hepatitis**	3 (1.2)	1 (0.4)	5 (1.8)	5 (1.8)	3 (1.1)	3 (1.1)
○ **Hypophysitis**	6 (2.3)	4 (1.6)	2 (0.7)	1 (0.4)	1 (0.4)	1 (0.4)
○ **Pneumonitis**	1 (0.4)	1 (0.4)	5 (1.8)	1 (0.4)	1 (0.4) 0	1 (0.4) 0
○ **Type 1 diabetes mellitus**	0	0	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
○ **Uveitis**	0	0	3 (1.1)	0	1 (0.4)	0
○ **Myositis**	1 (0.4)	0	2 (0.7)	0	0	0
○ **Nephritis**	1 (0.4)	1 (0.4)	1 (0.4)	0	0	0 0

** The relationship between an adverse event and a study drug was attributed by the investigator. Events are listed in order of descending frequency in the group receiving pembrolizumab every 2 weeks, except for hypothyroidism, hyperthyroidism, and colitis, which are reported as adverse events of special interest.*

† The listed adverse events of special interest include related terms and are provided regardless of attribution to a study drug. Events are listed in order of descending frequency in the group receiving pembrolizumab every 2 weeks.

KEYNOTE-001 Part D: Adverse reactions

A summary of AEs from KEYNOTE-001 (Part D)[70] is provided in Table 61 below. Grade 3-5 AEs occurred in 37.3% of patients treated with the 2 mg/kg Q3W dose of pembrolizumab. Relatively few patients discontinued treatment due to an AE.

Table 61: KEYNOTE-001 Part D – AE summary

	Pembrolizumab 2 mg/kg Q3W		Pembrolizumab 10 mg/kg Q3W	
	n	(%)	n	(%)
Subjects in population	51		52	
with one or more adverse events	51	(100.0)	51	(98.1)
with no adverse event	0	(0.0)	1	(1.9)
with drug-related† adverse events	44	(86.3)	47	(90.4)
with grade 3-5 adverse events	19	(37.3)	22	(42.3)
with grade 3-5 drug-related adverse events	12	(23.5)	2	(3.8)
with serious adverse events	14	(27.5)	18	(34.6)
with serious drug-related adverse events	7	(13.7)	3	(5.8)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	2	(3.9)	5	(9.6)
discontinued due to a drug-related adverse event	1	(2.0)	3	(5.8)
discontinued due to a serious adverse event	2	(3.9)	2	(3.8)
discontinued due to a serious drug-related adverse event	1	(2.0)	1	(1.9)

Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
(Database cut-off date: 18APR2014)

Table 62 displays the number and percentage of patients with AEs (Incidence > 10% in one or more treatment groups) in Part D.

Table 62: KEYNOTE-001 Part D - Subjects with AEs (incidence ≥ 10% in one or more treatment groups) (APaT population)

	Pembrolizumab 2 mg/kg Q3W		Pembrolizumab 10 mg/kg Q3W	
	n	**(%)**	**N**	**(%)**
Subjects in population	51		52	
• with one or more adverse events	51	(100.0)	51	(98.1)
• with no adverse events	0	(0.0)	1	(1.9)

Blood and lymphatic system	**11**	**(21.6)**	**13**	**(25.0)**
• Anaemia	9	(17.6)	7	(13.5)
Cardiac disorders	**5**	**(9.8)**	**6**	**(11.5)**
Ear and labyrinth disorders	**5**	**(9.8)**	**7**	**(13.5)**
Endocrine disorders	**12**	**(23.5)**	**4**	**(7.7)**
• Hypothyroidism	8	(15.7)	**4**	**(7.7)**
Eye disorders	**8**	**(15.7)**	**6**	**(11.5)**
Gastrointestinal disorders	**35**	**(68.6)**	**39**	**(75.0)**
• Abdominal pain	5	(9.8)	6	(11.5)
• Abdominal pain upper	1	(2.0)	6	(11.5)
• Constipation	11	(21.6)	13	(25.0)
• Diarrhoea	17	(33.3)	16	(30.8)
• Nausea	15	(29.4)	24	(46.2)
• Vomiting	9	(17.6)	8	(15.4)
General disorders and administration site conditions	**35**	**(68.6)**	**42**	**(80.8)**
• Asthenia	8	(15.7)	11	(21.2)
• Chills	3	(5.9)	5	(9.6)
• Fatigue	20	(39.2)	30	(57.7)
• Influenza like illness	3	(5.9)	6	(11.5)
• Oedema peripheral	7	(13.7)	9	(17.3)
• Pyrexia	5	(9.8)	5	(9.6)
Infections and infestations	**24**	**(47.1)**	**31**	**(59.6)**
• Nasopharyngitis	9	(17.6)	8	(15.4)
• Upper respiratory tract infection	4	(7.8)	3	(5.8)
• Urinary tract infection	5	(9.8)	6	(11.5)
Injury, poisoning and procedural complications	**11**	**(21.6)**	**3**	**(5.8)**
Investigations	**25**	**(49.0)**	**23**	**(44.2)**
• Weight decreased	6	(11.8)	7	(13.5)
Metabolism and nutrition disorders	**18**	**(35.3)**	**22**	**(42.3)**
• Decreased appetite	7	(13.7)	10	(19.2)
Musculoskeletal and connective tissue disorders	**34**	**(66.7)**	**34**	**(65.4)**
• Arthralgia	16	(31.4)	16	(30.8)
• Back pain	9	(17.6)	9	(17.3)
• Muscular weakness	2	(3.9)	0	(0.0)
• Musculoskeletal pain	4	(7.8)	7	(13.5)
• Myalgia	5	(9.8)	13	(25.0)
• Pain in extremity	9	(17.6)	7	(13.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4**	**(7.8)**	**2**	**(3.8)**
Nervous system disorders	**20**	**(39.2)**	**27**	**(51.9)**
• Dizziness	4	(7.8)	4	(7.7)
• Headache	6	(11.8)	16	(30.8)
Psychiatric disorders	**11**	**(21.6)**	**9**	**(17.3)**
• Insomnia	4	(7.8)	6	(11.5)
Renal and urinary disorders	**5**	**(9.8)**	**7**	**(13.5)**
Reproductive system and breast disorders	**4**	**(7.8)**	**3**	**(5.8)**
Respiratory, thoracic and mediastinal disorders	**27**	**(52.9)**	**28**	**(53.8)**
• Cough	15	(29.4)	15	(28.8)

• Dyspnoea	10	(19.6)	12	(23.1)
Skin and subcutaneous tissue disorders	**30**	**(58.8)**	**35**	**(67.3)**
• Night sweats	4	(7.8)	1	(1.9)
• Pruritus	10	(19.6)	17	(32.7)
• Rash	12	(23.5)	14	(26.9)
• Vitiligo	5	(9.8)	7	(13.5)
Vascular disorders	**9**	**(17.6)**	**12**	**(23.1)**

Every patient is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Malignant neoplasm progression' not related to the drug is excluded.
(Database cut-off date: 18APR2014)

4.12.3 Studies that report additional adverse reactions to those reported in section 4.2

The search strategy used to identify studies which reported AEs was consistent with that described in section 4.1 (see Appendix 15).

Table 63 below provides details of the drug-related AEs according to dosing cohort[74] from KEYNOTE-001 Part B1 – APaT population. Of the 135 patients who received at least one dose of pembrolizumab, 64% of those receiving the 2 mg/kg Q3W dose reported drug-related adverse events of any grade, and 9% reported grade 3 or 4 drug-related adverse events.

Adverse events of particular interest were of an inflammatory or autoimmune nature. Treatment- related pneumonitis was reported in 5% of the patients receiving pembrolizumab 2 mg/kg Q3W; none of the cases were grade 3 or 4.

Although treatment-related diarrhoea was reported in 27% of the patients treated with the 2 mg/kg Q3W dose, no cases of grade 3-4 treatment-related diarrhoea were reported in patients treated with this dose.

Treatment-related hypothyroidism was reported in 5% of the patients treated with the 2 mg/kg Q3W dose, and was effectively managed with thyroid-replacement therapy.

Table 63: KEYNOTE-001 Part B1 - Drug-related AEs that occurred in at least 1% of patients (APaT population)

Drug related adverse events	**2.0 mg/kg Q3W**	
	n (%)	**grade 3-4**
Patients in population	22	
with one or more adverse events	14 (63.6)	2 (9.1)
Blood And Lymphatic System Disorders		
Anemia	0 (0.0)	0 (0.0)

Leukopenia	1 (4.5)	0 (0.0)
Thrombocytopenia	2 (9.1)	0 (0.0)
Endocrine Disorders		
Hypothyroidism	1 (4.5)	0 (0.0)
Eye Disorders		
Dry Eye	0 (0.0)	0 (0.0)
Uveitis	0 (0.0)	0 (0.0)
Visual Impairment	1 (4.5)	0 (0.0)
Gastrointestinal Disorders		
Abdominal Discomfort	0 (0.0)	0 (0.0)
Abdominal Distension	0 (0.0)	0 (0.0)
Abdominal Pain	1 (4.5)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)
Diarrhoea	6 (27.3)	0 (0.0)
Dry Mouth	0 (0.0)	0 (0.0)
Nausea	2 (9.1)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)
General Disorders		
Asthenia	0 (0.0)	0 (0.0)
Chills	1 (4.5)	0 (0.0)
Fatigue	2 (9.1)	0 (0.0)
Oedema Peripheral	0 (0.0)	0 (0.0)
Night Sweats	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)
Infections		
Diverticulitis	0 (0.0)	0 (0.0)
Influenza	0 (0.0)	0 (0.0)
Laboratory abnormalities		
ALT Increased	0 (0.0)	0 (0.0)
AST Increased	1 (4.5)	0 (0.0)
Blood Alkaline Phosphatase Increased	0 (0.0)	0 (0.0)
Blood Cholesterol Increased	0 (0.0)	0 (0.0)
Blood Creatinine Increased	0 (0.0)	0 (0.0)
Platelet Count Decreased	0 (0.0)	0 (0.0)
Transaminases Increased	0 (0.0)	0 (0.0)
Weight Decreased	0 (0.0)	0 (0.0)
Metabolism And Nutrition Disorders		
Decreased Appetite	1 (4.5)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)
Hyperglycemia	1 (4.5)	0 (0.0)
Musculoskeletal And Connective Tissue Disorders		
Arthralgia	1 (4.5)	0 (0.0)
Arthritis	0 (0.0)	0 (0.0)
Back Pain	0 (0.0)	0 (0.0)
Muscle Spasms	1 (4.5)	0 (0.0)
Muscular Weakness	0 (0.0)	0 (0.0)
Myalgia	1 (4.5)	0 (0.0)
Neck Pain	0 (0.0)	0 (0.0)
Pain In Extremity	1 (4.5)	0 (0.0)
Nervous System Disorders		
Balance Disorder	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)
Dysgeusia	1 (4.5)	0 (0.0)
Headache	1 (4.5)	0 (0.0)
Neuropathy Peripheral	0 (0.0)	0 (0.0)
Psychiatric Disorders		
Confusion	0 (0.0)	0 (0.0)

Renal And Urinary Disorders		
Renal failure	0 (0.0)	0 (0.0)
Respiratory Disorders		
Cough	2 (9.10	0 (0.0)
Dyspnea	1 (4.5)	0 (0.0)
Nasal Congestion	0 (0.0)	0 (0.0)
Pneumonitis	0 (0.0)	0 (0.0)
Productive Cough	0 (0.0)	0 (0.0)
Skin And Subcutaneous Tissue Disorders		
Eczema	0 (0.0)	0 (0.0)
Erythema	1 (4.5)	0 (0.0)
Hair Color Changes	0 (0.0)	0 (0.0)
Pruritus	4 (18.2)	1 (4.5)
Rash	3 (13.6)	1 (4.5)
Rash Maculo-Papular	0 (0.0)	0 (0.0)
Vitiligo	1 (4.5)	0 (0.0)
Vascular Disorders		
Hot Flush	0 (0.0)	0 (0.0)

ALT: alanine aminotransferase; AST: aspartate aminotransferase

4.12.4 Brief overview of the safety of the technology in relation to the decision problem

Results from KEYNOTE-006 demonstrate that pembrolizumab was well-tolerated, exhibiting generally low grade toxicities that were managed satisfactorily by treatment interruption, steroid treatment (generally at low doses), and/or infrequent need for treatment discontinuation (e.g. for only 5% of pembrolizumab treated subjects). Grade 3-5 drug-related AEs occurred in a greater percentage of subjects in the ipilimumab arm (20%) compared to subjects treated with pembrolizumab 10 mg/kg Q2W (13%) or pembrolizumab 10 mg/kg Q3W (10%) (Table 56).

Serious AEs, regardless of causality, were higher in frequency in subjects treated with ipilimumab (30%) compared with subjects treated with pembrolizumab 10 mg/kg Q3W (25%) or pembrolizumab 10 mg/kg Q2W (26%) (Table 56). Drug-related SAEs were greater in incidence in the ipilimumab treatment arm (18%) compared with 7% and 11% in the pembrolizumab 10 mg/kg Q3W and 10 mg/kg Q2W arms, respectively (Table 56). Discontinuation due to drug-related AEs was greater in the ipilimumab arm (9%) than in either of the pembrolizumab arms (7% in the 10 mg/kg Q3W and 4% in the 10 mg/kg Q2W arm (Table 56). No differences were seen between the two dose schedules used in the respective pembrolizumab treatment arms across a broad range of analyses including total AEs, SAEs, AEs leading to discontinuation, grade 3-5 AEs or drug-related AEs.[23]

To more specifically assess those AEs most likely to be related to the immune activity of pembrolizumab, AEOSIs regardless of investigator attribution or assessment of immune-relatedness were evaluated. AEOSIs were seen in 109 of 555 subjects (19.6%) on the combined pembrolizumab arms versus 47 of 256 (18.4%) on the ipilimumab arm. This composite frequency likely overestimates truly immune-mediated AEs since it includes events regardless of attribution. Most AEOSIs in the combined pembrolizumab arms were Grade 1-2 in severity since only 30 of 555 (5.4%) had Grade 3-5 AEOSIs (Table 59). In comparison, 30 of 256 (11.7%) subjects) in the ipilimumab arm had Grade 3-5 AEOSIs (Table 59). Only 2.7% of subjects treated with pembrolizumab discontinued therapy due to any AEOSI (regardless of causality) versus 5.5% in subjects treated with ipilimumab (Table 59). Overall, most AEOSIs were manageable with treatment interruption and systemic corticosteroids as specifically indicated.

AEOSIs with a higher incidence in the pembrolizumab arms were generally of lower grades, and led to fewer discontinuations compared with those with a higher incidence in the ipilimumab arm. For example, while the overall incidence of hypothyroidism and hyperthyroidism were 8.7% and 3.2%, respectively, in the pembrolizumab 10 mg/kg Q3W arm, there was no Grade 3-5 hypothyroidism or hyperthyroidism reported (Table 60). No patients discontinued treatment due to hypo- or hyperthyroidism, and patients were managed by hormone replacement therapy (HRT) and temporary treatment interruption, respectively.[23] A majority of cases of hyperthyroidism resolved without treatment interruption.

AEOSIs with a higher incidence in the ipilimumab arm were generally of higher grades and led to high rates of discontinuation compared with AEOSIs with a higher incidence in the combined pembrolizumab arms. Grade 3-5 colitis was seen in 7.0% compared with the 8.2% overall incidence. Grade 3-5 hypophysitis was seen in 1.6% compared with the 2.3% overall incidence (Table 60). Instances of colitis in the ipilimumab treatment arm was generally a SAE, occurred early, often required treatment discontinuation, and generally required treatment with high dose steroids.[23]

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

Efficacy results from KEYNOTE-006, a phase III RCT, demonstrate that pembrolizumab is superior to ipilimumab in the population of patients with advanced melanoma, previously untreated with ipilimumab (i.e. ipilimumab-naïve patients).

Since the OS results at IA2 surpassed the pre-specified efficacy boundary (alpha level 0.005 using Hochberg step-up procedure), KEYNOTE-006 was stopped early for efficacy at the recommendation of the DMC, and the results were unblinded. At IA2, the HR for OS was 0.69 (p=0.00358) in the pembrolizumab 10 mg/kg Q3W arm over the ipilimumab arm, favouring pembrolizumab (Table 27;

Figure **11**). OS between the two pembrolizumab arms was also shown to be comparable (HR 0.91, p=0.51319). KEYNOTE-006 will continue evaluation of safety and survival follow-up until the pre-specified final analysis, which is scheduled to occur when all subjects have been followed for 21 months (03-Dec-2015) or approximately 435 deaths have occurred, whichever occurs first. Investigators have been made aware that the study has met the primary endpoints of OS and PFS.

The 12-month survival rates were improved by 10% for subjects receiving pembrolizumab 10 mg/kg Q3W compared to ipilimumab (68% for pembrolizumab 10 mg/kg Q3W [95% CI: 62.5%, 73.6%], compared to 58% for ipilimumab [95% CI: 51.8%, 64.0%] (Table 28)). It is notable that the 12-month OS rates for ipilimumab observed in KEYNOTE-006 were better than has been previously reported in Phase 3 ipilimumab studies. For example, in the Phase 3 study of ipilimumab + dacarbazine compared to dacarbazine alone,[33] ipilimumab had a median OS of 11.2 months and a 12-month OS rate of 47%.

Pembrolizumab improved PFS compared to ipilimumab (based on central (IRO) assessment per RECIST 1.1) with an HR of 0.58 in both pembrolizumab arms over the ipilimumab arm (p <0.00001 in both comparisons, favouring pembrolizumab).The median PFS was 4.1 months in the pembrolizumab 10 mg/kg Q3W arm and 2.8 months in the ipilimumab arm (Table 22). There was no difference between the two pembrolizumab arms in PFS (HR=0.97, p=0.76 when the two arms were compared). The PFS curves separated by the time of the first assessment (12 weeks), with the separation increasing thereafter, reflected by a 6-month PFS rate of 46.4% in the pembrolizumab 10 mg/kg Q3W arm compared to 26.5% in the ipilimumab arm (Table 22; Figure 8).

Pembrolizumab resulted in a higher confirmed ORR (assessed by central (IRO) review based on RECIST 1.1) compared to the ipilimumab arm (ORR of 32.9% in the pembrolizumab 10 mg/kg Q3W arm compared to 11.9% in the ipilimumab arm (Table 29)). Improvement of ORR with pembrolizumab is approximately 3 fold, and the difference is statistically significant. The responses appeared to be durable in all groups, with 97.0% of responses in the pembrolizumab 10 mg/kg Q3W arm ongoing and 87.8% of responses in the ipilimumab arm ongoing at the data cut-off for IA1 (Table 31).

There were no meaningful differences in efficacy observed in KEYNOTE-006 between the two pembrolizumab regimens, 10 mg/kg Q2W and 10 mg/kg Q3W. The lack of a dose-response relationship corroborates prior results from the randomised Part D cohort in KEYNOTE-001 which was conducted in an ipilimumab naïve population. Additionally, it

reinforces findings from Part B2 of KEYNOTE 001 and the RCT KEYNOTE-002 trial (both concerning the population of patients previously treated with ipilimumab), in which pembrolizumab was administered at different doses ranging from 2 mg/kg Q3W to 10 mg/kg Q2W with no impact on outcomes.

Safety findings from KEYNOTE-006 showed that pembrolizumab, as compared with ipilimumab resulted in fewer high-grade toxic events in patients with advanced melanoma. Pembrolizumab was associated with fewer AEs, with milder AEs with later onset, and with AEs with less therapeutic impact as compared with ipilimumab (section 4.12.4). Only a small number of AEs led to pembrolizumab treatment alterations. The 3-fold longer exposure to treatment in the pembrolizumab arms versus the ipilimumab arm complicated some aggregated analyses, since unadjusted comparisons of the two treatments could imply approximate equivalence in some analyses. For example, grade 3-5 AEs occurred in 37% of subjects treated with ipilimumab versus 33% of subjects treated with pembrolizumab 10 mg/kg Q3W (and 38% of subjects treated with pembrolizumab 10 mg/kg Q2W). Accordingly, because of the difference in treatment time and exposure, three adjusted analyses were performed including the following: a comparison of events during active treatment for ipilimumab and pembrolizumab in the first three months of administration; an evaluation as a function of exposure; and an evaluation as a function of time to first AE. All three adjusted analyses demonstrated fewer AEs in pembrolizumab subjects (Appendix 14).

In conclusion, the results from KEYNOTE-006, an RCT comparing two immune checkpoint inhibitors, validates that pembrolizumab significantly improved OS, PFS, and ORR of melanoma subjects compared to ipilimumab. The OS results at IA2 are both statistically significant for pembrolizumab, and clinically meaningful. The data from KEYNOTE-006 reinforces the clinical superiority of pembrolizumab compared to ipilimumab in terms of efficacy and safety, as well as the lack of a dosing schedule effect on pembrolizumab (Q2W vs. Q3W).

4.13.2 Discussion of the strengths and limitations of the clinical evidence base for the technology

Internal Validity

The co-primary efficacy endpoints of the randomised KEYNOTE-006 study were PFS and OS. Both are clinically relevant endpoints that were directly referenced in the final scope for this appraisal and the decision problem. The endpoints selected are consistent with those implemented in studies of other therapeutic agents in the population of advanced melanoma.

The definition of progression when evaluating the co-primary endpoint of PFS in KEYNOTE-006 followed an established response evaluation criteria (RECIST 1.1) in the primary efficacy analysis, in line with European guidance.[95]

Crossover was not permitted within the study design of KEYNOTE-006, so a clear comparison of the efficacy of pembrolizumab versus ipilimumab was possible based on unadjusted analysis.

HRQoL was an exploratory endpoint of the study, with changes from baseline in patients treated with pembrolizumab compared to patients treated with chemotherapy recorded using both the preferred measure of EQ-5D according to the NICE reference case, in addition to the cancer specific EORTC-QLQC30 (see section 5.4).

Part D of KEYNOTE-001 assessed the clinically relevant endpoint of RR as a primary endpoint. Although KEYNOTE-001 does not provide comparative efficacy versus a comparator of interest, it was a randomised study and does provide useful data supporting the comparability of efficacy between the licensed dose of pembrolizumab (2 mg/kg) and the dose assessed in KEYNOTE-006 (10 mg/kg).

External validity

The pivotal clinical trial KEYNOTE-006 is a global study that was conducted in 16 countries, including the UK. English patients with advanced melanoma, who were naïve to previous treatment with ipilimumab, were represented within the patient population considered in this study.

KEYNOTE-006 assessed two different dosing schedules (Q2W and Q3W) of the 10 mg/kg dose of pembrolizumab, compared with ipilimumab 3 mg/kg Q3W (up to a maximum of 4 cycles). The duration of the pembrolizumab IV infusion is 30 minutes, which has the advantage of being substantially shorter that the infusion time for ipilimumab (90 minutes). The pembrolizumab dosing regimens assessed in KEYNOTE-006 differ from the licensed dose (2mg/kg) at a Q3W dosing schedule. Nevertheless clinical data supporting the efficacy profile of the licensed dose of pembrolizumab (2 mg/kg) in an ipilimumab-naïve patient population has been presented at the end of section 4.7. The clinical efficacy results from KEYNOTE-001 Part D demonstrate the comparability of results from the 10 mg/kg Q3W dose and the 2 mg/kg Q3W dose in an ipilimumab-naïve population (section 4.7). Additionally results from KEYNOTE-006 demonstrate no significant difference in efficacy outcomes between the Q2W and Q3W dosing schedules of the 10 mg/kg dose (see section 4.7).

Patients with $BRAF^{V600}$ mutations with high LDH levels and symptomatic or rapidly progressive disease were not enrolled in KEYNOTE-006 unless they had received previous anti-BRAF targeted therapy, because targeted anti-BRAF agents can have a rapid clinical benefit in this population of patients.[5] The treatment pathway for melanoma patients with $BRAF^{V600}$ mutations and specifically, the optimum sequencing of immunotherapies and BRAF or MEK inhibitors remains unknown at present, and will require further RCTs to address this issue. Yet, results from KEYNOTE-006 demonstrated that $BRAF^{V600}$ status did not affect the benefit of pembrolizumab over ipilimumab in this study population.

Life expectancy of people with advanced melanoma in England

Full details concerning the life expectancy of UK patients with metastatic melanoma have been provided in section 3.4 of the submission and are summarised in Table 64 below. Information concerning the estimated number of people with the particular therapeutic indication for which the technology is being appraised is also presented in section 3.4.

Table 64: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS is lower than 24 months: • Treatment-naïve patients treated with ipilimumab experience a median OS of 13.5 months, and 11.4 months if they have been previously treated.[9] • Median OS for treatment-naïve patients with $BRAF^{V600}$ positive mutations treated is 13.6 months[8] with vemurafenib and 20.1 months for dabrafenib.[96]
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	Pembrolizumab offers an extension to life of at least 3 months compared to ipilimumab, vemurafenib and dabrafenib: • The average number of life years gained with pembrolizumab as estimated by the economic model is 5.08 years, compared to 4.37 life years with ipilimumab, 3.41 with dabrafenib and 2.74 with vemurafenib.
The treatment is licensed or otherwise indicated for small patient populations	The estimated number of patients eligible for pembrolizumab in England is expected to be approximately 1,304 patients in 2016 - see Table 5 and sections 3.4 and 6 of submission

4.14 Ongoing studies

KEYNOTE-006: As OS was positive at IA2 of KEYNOTE-006, no formal OS analysis will be conducted at the planned final analysis. However, patients will continue to be followed up and long-term survival for this study will be updated as deemed appropriate.

PFS results presented in this submission are from IA1. PFS results from IA2 will be available in the next 4 weeks.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Strategies used to retrieve cost-effectiveness studies relevant to decision-making in England

Relevant cost-effectiveness studies from the published literature and from unpublished data were identified through a systematic literature search carried out during the period between 16 July 2014 and 23 July 2014, and updated in March 2015, for patients who are naïve to treatment with ipilimumab and advanced melanoma.

The first stage in the review was to identify all relevant economic evidence for the comparator treatments by implementing comprehensive searches. The following research questions were posed in accordance with the decision problem:

- What is the cost-effectiveness of comparator therapies to pembrolizumab in treating patients with advanced melanoma?
- What is the health related quality of life (in terms of utilities) associated with advanced melanoma?
- What are the resource requirements and costs associated with the treatment of advanced melanoma?

A comprehensive literature search relative to these three research questions was carried out using several databases:

- MEDLINE and MEDLINE In-process (using Ovid platform) - 1946 to July 2014 – searches updated in March 2015
- EconLit: 1886 to July 2014 – searches updated in March 2015
- EMBASE - 1974 to July 2014 – searches updated in March 2015
- The Cochrane Library, including NHS EED and HTA databases

Hand searches were also performed from the American Society of Clinical Oncology (ASCO), ESMO and ISPOR. They were constrained to the most recent 2 years (from July 2014) and updated searches were conducted in March 2015.

In addition to the formal literature search and hand searches, the National Institute for Health and Care Excellence (NICE) website was searched to identify relevant information from previous submissions not otherwise captured.

Table 65 provides details relative to the eligibility criteria for the cost-effectiveness literature search. Details of the search strategies conducted for the health related quality of life and utilities and resource and costs are provided in Appendix 21 and Appendix 23.

To determine which studies were eligible, explicit inclusion and exclusion criteria were applied when evaluating the literature search results. These selection criteria are detailed below for the cost-effectiveness search. The other two literature searches relative to the health related quality of life and utilities and resource and costs are provided Appendix 21 and Appendix 23 and are detailed in sections 5.4 and 5.5.

Table 65: Inclusion and exclusion criteria for cost-effectiveness studies

Criteria	Inclusion	Exclusion	Rationale
Population	Patients with advanced melanoma who are naïve to treatment with ipilimumab.	None	The population criteria are broader than unresectable/metastatic melanoma. This decision was taken to ensure the review captured sufficient relevant information to be of use.
Intervention/ Comparator	Any medical treatment of advanced melanoma, or best supportive care, no treatment or placebo.	Non-pharmacological interventions	To allow all studies with relevant interventions to be captured
Outcomes	Studies including a comparison of costs between the intervention and comparator arms. Results should also include either incremental QALYs (or another measure of health outcome/clinical effectiveness), or be structured with a cost-minimisation argument.	Cost-only outcomes (without a cost-minimisation argument, e.g. burden of illness studies).	To identify relevant cost-effectiveness outcomes
Study type	Full economic evaluations, comparing at least two interventions in terms of: cost-consequence, cost-minimisation, cost-effectiveness, cost-utility or cost-benefit	Reviews (systematic or otherwise), letters and comment articles.	To identify relevant cost-effectiveness studies
Publication type	Economic evaluations	Burden of illness studies	Primary study articles were required
Language	Studies for which a full text version is available in English.	Not available in English	To ensure the studies could be correctly understood and

Criteria	Inclusion	Exclusion	Rationale
			interpreted
Other	Studies must present sufficient detail of the methodology used and provide extractable results.	Studies that fail to present sufficient methodological detail, such that the methods cannot be replicated or validated. Studies that fail to present extractable results.	To ensure methods could be replicated To ensure results could be validated
Key: *QALY, Quality-adjusted life year.*			

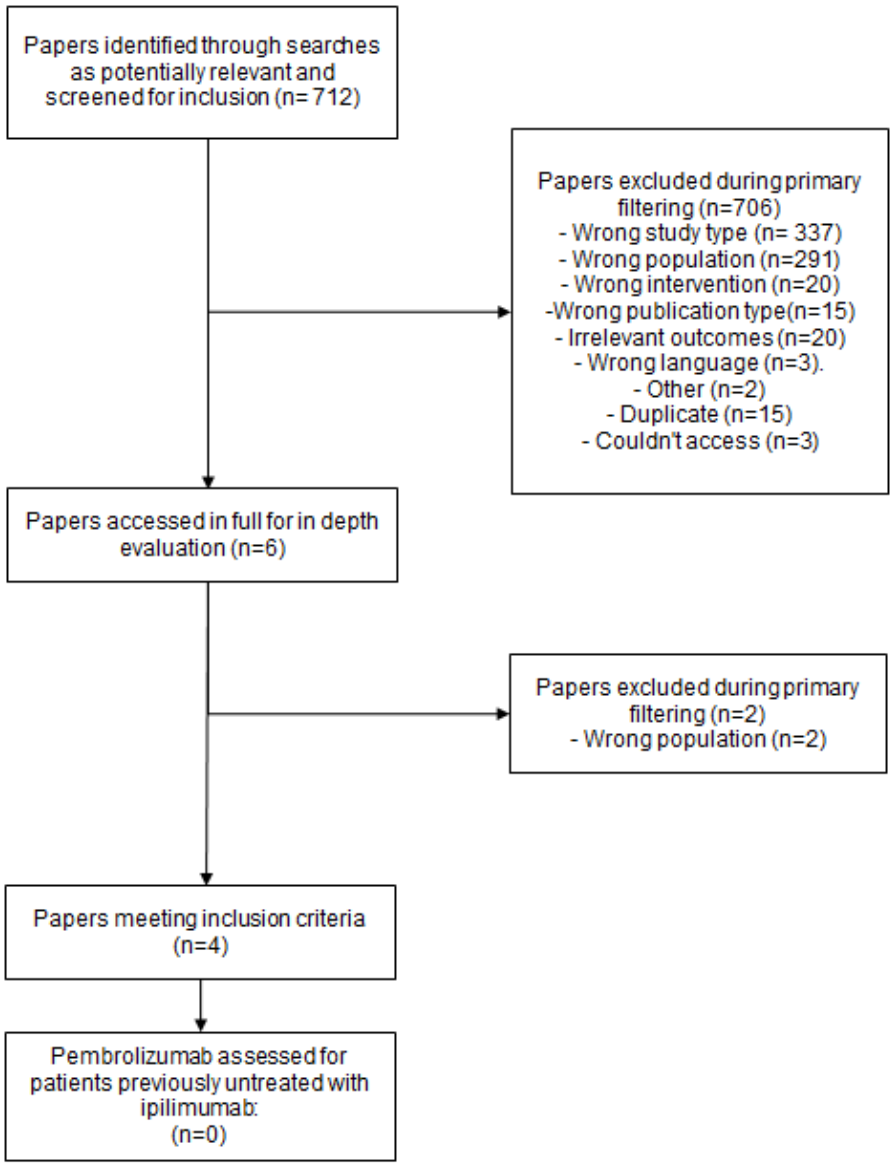
The above searches were conducted following the methodology for systematic review developed and published in 2009 by the Centre for Reviews and Dissemination (University of York).[97]

5.1.2 Brief overview of each cost-effectiveness study only if it is relevant to decision-making in England

Of a total of 712 papers identified in the cost-effectiveness search, no cost-effectiveness studies assessing pembrolizumab for patients previously untreated with ipilimumab were found that met all the inclusion criteria (see Figure 20).

A summary list of published cost-effectiveness studies has not been compiled as no cost-effectiveness studies assessing pembrolizumab for patients previously untreated with ipilimumab that met all the inclusion criteria were identified. The lack of identified cost-effectiveness studies in this setting can probably be explained by the amount of time since the last recent positive NICE recommendation of ipilimumab for previously untreated unresectable melanoma patients (TA 319 July 2014).[3]

Figure 20: PRISMA diagram CEA studies



5.1.3 Complete quality assessment for each relevant cost-effectiveness study identified

Not applicable as no cost-effectiveness study meeting all the inclusion criteria was identified.

5.2 De novo analysis

5.2.1 Patient population

The patient population included in the economic evaluation comprises patients with unresectable or metastatic melanoma previously untreated with ipilimumab (see Appendix 1). It is also in line with the population defined in the final appraisal scope.[98] Given that the type of comparators differed depending on the BRAF mutation status of patients, two sub-populations were considered: patients with $BRAF^{V600}$ positive mutations and patients with $BRAF^{V600}$ wild type mutations.

The main body of clinical evidence for pembrolizumab was derived from the KEYNOTE-006 trial, in which included patients who had not been previously treated with ipilimumab or another PD-1 or PD-L1 inhibitor.[18] The justification for the choice of clinical evidence used in the economic model is presented in section 5.3.1.

The baseline characteristics of the patients included in the model are presented in Table 66. These are assumed equal for both the $BRAF^{V600}$ positive mutation and with $BRAF^{V600}$ wild type mutation subgroups since BRAF status did not seem to affect the benefit of pembrolizumab over ipilimumab in the KEYNOTE-006 clinical trial (see section 4.8).[18]

Table 66. Baseline characteristics of patients included in the model

Patient Characteristics	Mean	Distribution and CI	Reference / Source
Average age	60.3	Normal (59.34,61.26,)	KEYNOTE-006
Proportion patients male	0.60	Beta (0.56, 0.63)	KEYNOTE-006
Average patient weight (kg)	78.63	Normal (77.01, 80.25)	KEYNOTE-006 (European patients; see Appendix 30)
Average patient body surface area (m2)	1.91	Normal (1.16, 2.66)	KEYNOTE-002 - European patients
Proportion ECOG 0	68.7%	Not varied in sensitivity analysis*	KEYNOTE-006
Proportion ECOG 1	31.3%	Not varied in sensitivity analysis*	KEYNOTE-006
Proportion ECOG2	0.0%	Not varied in sensitivity analysis*	KEYNOTE-006
Proportion brain metastases	9.4%	Not varied in sensitivity analysis*	KEYNOTE-006
Proportion stage III	3.84%	Beta (2.64%, 5.24%)	KEYNOTE-006
Proportion stage IV	96.16%	Beta (94.76%, 97.36%)	KEYNOTE-006
Proportion m1c	65.3%	Not varied in sensitivity analysis*	KEYNOTE-006

*These characteristics were not varied in sensitivity analysis as they were used only in the algorithms to adjust the Kaplan-Meier data for comparator trials to estimate what the OS would have been if the patients included in the trials had presented similar baseline characteristics as patients in KEYNOTE-006 patients. The characteristics of the patients in the KEYNOTE-006 trial are known and are therefore not uncertain.

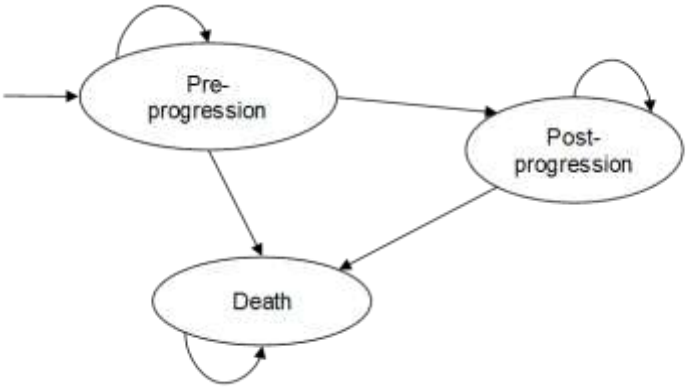
5.2.2 Model structure

Drawing upon the previous cost-effectiveness models submitted to NICE within advanced melanoma, a de-novo economic analysis was built as a 'partitioned-survival' model. Pembrolizumab was compared against ipilimumab and BRAF inhibitors vemurafenib and dabrafenib for patients with $BRAF^{V600}$ positive mutations. For patients with $BRAF^{V600}$ wild type mutations pembrolizumab was compared against ipilimumab. Dacarbazine was not included as a relevant comparator (see Table 1).

Consistent with the majority of economic models previously developed for NICE oncology submissions in advanced melanoma[2;16;17] the model consisted of three health states: pre-progression, post-progression and death (see Figure 21). This approach was also in line with the clinical endpoints assessed in the pembrolizumab clinical trials, in which OS and PFS were either primary[18] or secondary endpoints.[75;99] A cycle length of one week was considered sufficient to reflect the patterns of treatment administration and the transitions to disease progression and death; this cycle length was consistent with those reported in previous advanced melanoma submissions.[2;16;17]

Health states were mutually exclusive, meaning that patients could only be in one state at a time. All patients started in the pre-progression state. Transitions to the death state could occur from either pre-progression or post-progression, while death was an 'absorbing state'.

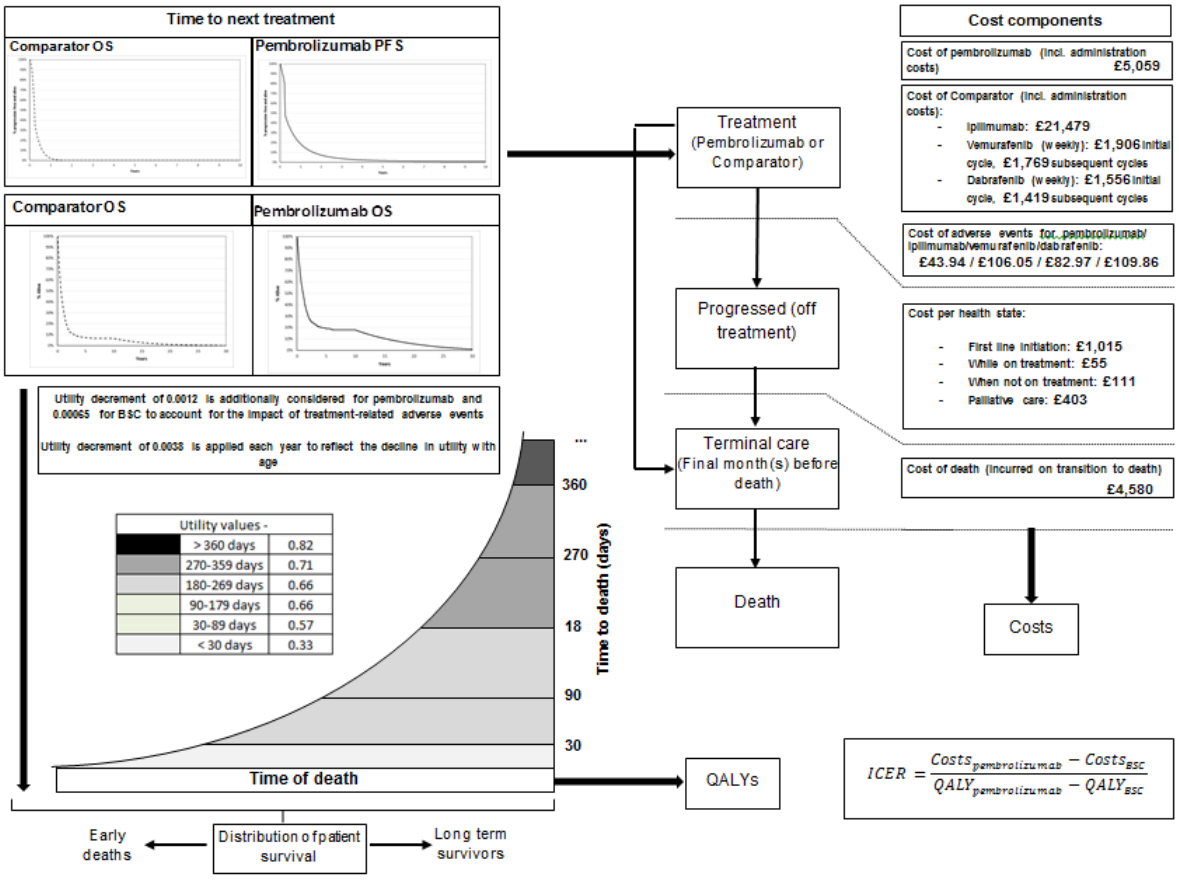
Figure 21. Model structure



In the model, patients were assumed to receive treatment until progression, in line with the licence for pembrolizumab.

To capture more accurately the impact of pembrolizumab upon costs and quality of life, the measurements considered in the base case analysis were based on time spent alive (as shown in Figure 22), rather than progression status. Time-to-death sub-health states were used to capture patients' quality of life as a function of how much lifetime patients had left until they eventually died. This approach was in line with the methodology used during the appraisal of ipilimumab in TA319.[3] The use of time-to-death sub-health states was implemented considering six health states: <30 days to death, 30-89 days to death, 90-179 days to death, 180-269 days to death, 270-359 days to death and >360 days to death, each associated with a specific utility value. Additionally, each of the non-absorbing health states had specific treatment, resource utilisation and AE costs.

Figure 22. Model structure



For the purpose of the model it was assumed that once patients progressed, no further subsequent active therapies were administered and patients only received palliative care. This was considered to be a simplification of reality but was justified based on the following:

- The decision problem of this appraisal is to determine whether the use of pembrolizumab in patients who have not previously received treatment with ipilimumab is efficacious and cost-effective. Considering explicitly further lines of

treatment leads to a different decision problem being considered, i.e. to determine the optimum sequence of treatments, which is not the focus of the appraisal.

- In TA319 the manufacturer attempted to model second-line active therapy and third-line BSC for patients progressing after first-line treatment. The approach was criticised by the ERG because of oversimplifying this issue and for making arbitrary assumptions in the absence of the data needed to model treatment sequencing. These assumptions were a major driver of the cost-effectiveness results and, as a consequence, the ERG recommended to consider a three-state model with BSC being the only second-line therapy considered.[3]

For our model, we assumed that BSC (which included 'no treatment' and conventional chemotherapies used in the UK for palliative purposes) was the only subsequent therapy administered after progression, independent of the treatment previously received. Similar efficacy and costs were assumed, to estimate the impact of first line therapies without the potential differential impact that the selection of different subsequently administered therapies could have on health benefits and costs.

The definition of the health states used in the model was based on the definitions conventionally used in oncology clinical trials and, specifically, the ones used in the pembrolizumab KEYNOTE-006 trial:

- Progressive disease was defined following the RECIST 1.1 criteria, i.e., at least a 20% increase in the sum of diameters of target lesions, and an absolute increase of at least 5 mm, or appearance of one or more new lesions.[78]
- Non-progressive disease reflected patients being alive and not in progressive disease (which included patients with complete response, partial response and stable disease).
- Death (absorbing health state)

5.2.3 Key features of the de novo analysis

Table 67: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	30 years	Lifetime horizon for the defined target population[100] (1% of patients treated with pembrolizumab are estimated to be alive after this period) In line with previous advanced melanoma submissions[2;16;17]
Cycle length	1 week	Sufficient to model the patterns of treatment administration, transitions to disease progression and OS. In line with previous advanced melanoma NICE submissions[2;3;16;17]

Factor	Chosen values	Justification
Half-cycle correction	Not applied to costs and health effects in the base case but in sensitivity analysis	Irrelevant, given cycle length[16;17]
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case[100]
Discount of 3.5% for utilities and costs	Yes	NICE reference case[100]
Perspective (NHS/PSS)	Yes	NICE reference case[100]
PSS, personal social services; QALYs, quality-adjusted life years		

5.2.4 Intervention technology and comparators

The intervention (i.e. pembrolizumab) was implemented in the model as per the licensed dosing regimen (i.e. 2 mg/kg as an IV infusion over 30 minutes every 3 weeks [Q3W]).

The appropriate comparators for pembrolizumab were dependent on whether patients presented $BRAF^{V600}$ positive mutations or not (as mentioned in section 3.3):

- For patients with $BRAF^{V600}$ wild type mutations the relevant comparator was ipilimumab.
- For patients with $BRAF^{V600}$ positive mutations the relevant comparators were ipilimumab and BRAF inhibitors (including vemurafenib and dabrafenib).

The dosing regimens applied for ipilimumab, vemurafenib and dabrafenib were in line with their corresponding SPCs:

- Ipilimumab (3mg/kg)[127] was assumed to be administered as an intravenous infusion over 90 minutes every three weeks. Each patient received up to four doses in total.
- Vemurafenib[128] was assumed to be administered as four tablets (960mg) twice daily.
- Dabrafenib[129] was assumed to be administered as a 150mg dose twice daily.

5.2.5 Discontinuation rules

According to the licensed indication, patients should be treated with pembrolizumab until disease progression is confirmed or unacceptable toxicity.

5.3 Clinical parameters and variables

5.3.1 Clinical data incorporated in the model

Data from the Phase III randomised-controlled KEYNOTE-006 trial was used to estimate the patients' baseline characteristics, the proportion of patients under the different health states (based on PFS and OS data), the proportion of patients experiencing AEs and the utilities used to populate the model. The licence for pembrolizumab will cover a wider population than the population of patients previously untreated with ipilimumab; another NICE STA focused on the sub-population not covered by this submission (i.e. patients who have been previously treated with ipilimumab [ID760]) is currently ongoing.[22] Only data from the KEYNOTE-006 trial was finally incorporated into the economic model since this was a Phase III randomised clinical trial with head-to-head comparisons of pembrolizumab against ipilimumab, one of its relevant comparators.

The KEYNOTE-006 trial included a dose of pembrolizumab of 10mg Q3W, whereas the licensed dose will be 2mg/kg Q3W. Both of these doses of pembrolizumab were equivalent as evaluated in the relevant patient population in the KEYNOTE-001 trial (see section 4.7). The base case analysis therefore conservatively assumes that the dose used in the KEYNOTE-006 trial can be used as a proxy for the expected licensed dose, i.e. assuming equal efficacy of the 2mg/kg Q3W and 10mg/kg Q3W doses. A scenario analysis is provided whereby the HRs obtained from the relevant population of the KEYNOTE-001 trial were applied.

For the cost-effectiveness assessment evaluating the population of patients with $BRAF^{V600}$ wild type mutations, the clinical data was mainly derived from the KEYNOTE-006 trial and published long-term data from ipilimumab.[9] Alternative methods to the standard parametric curve fit were explored to extrapolate survival beyond the trial period. A combination of the KEYNOTE-006 trial data for the first 13 weeks and then parametric curves fit to the KEYNOTE-006 data from Week 13 onwards were used to estimate PFS for pembrolizumab and ipilimumab, For OS, KEYNOTE-006 Kaplan-Meier data was used for the first year and then external data were used to estimate longer-term OS given that the curves fit to the KEYNOTE-006 trial data were not clinically plausible (see section 5.3.3).

The long term survival benefit of ipilimumab has been previously recognised by NICE.[2;3] In KEYNOTE-006 pembrolizumab showed a significant improvement in both PFS and OS compared to ipilimumab among patients previously untreated with ipilimumab.[18] It is expected that this improvement will be maintained in the long term. A pooled analysis of individual patient data derived from ten prospective and two retrospective studies evaluating

long term outcomes associated with treatment with ipilimumab has been recently published by Schadendorf *et al*.[9] The study demonstrated a survival benefit plateauing at 3 years out of 7 years among treatment naïve patients (the extent of the data available for analysis for this subpopulation). Making use of the previous information, pembrolizumab OS was extrapolated in the base case analysis by assuming similar conditional survival rates as those observed for ipilimumab among treatment-naïve patients. This was achieved by assuming the same proportion of patients die between time t and t+1 for both pembrolizumab and ipilimumab and applying this to the proportion of patients still alive on each treatment arm. A summary of the clinical evidence used for pembrolizumab in the model and the corresponding strengths and weaknesses is presented in Appendix 18.

For the cost-effectiveness assessment of pembrolizumab compared to ipilimumab, vemurafenib and dabrafenib for patients with $BRAF^{V600}$ positive mutations, we used the published clinical trial data from each of the relevant comparator trials. The KEYNOTE-006 trial,[18] the BRIM-3 trial[8;101] and BREAK-3 trial[30;96] were therefore used for comparisons against ipilimumab, vemurafenib and dabrafenib, respectively. This allowed us to apply adjustment algorithms to OS Kaplan-Meier data[3;102] to account for the different baseline characteristics observed across trials.

Two adjustment algorithms were available to account for differences in baseline characteristics across trials. In TA319 an algorithm was developed using only data from two arms of patients receiving ipilimumab. It is unclear whether this algorithm is only relevant for adjustments conducted on different populations receiving ipilimumab. Therefore, the resulting adjustment equation may not be generalizable. The Korn algorithm[102] was based on a meta-analysis of 42 Phase II trials (with 70 trial arms) which accounted for between-trial (-arm) variability in prognostic variables.[102] Therefore, in the base case we used the Korn algorithm. The impact of using the algorithm developed in TA319[3] was assessed as part of sensitivity analyses.

A network meta-analysis of time-to-event data was conducted to compare PFS and OS of pembrolizumab, ipilimumab, vemurafenib and dabrafenib for the treatment of patients with $BRAF^{V600}$ positive mutations (see section 4.10). This analysis presented limitations, mainly related to differences in patients' baseline characteristics between the pembrolizumab, ipilimumab, vemurafenib and dabrafenib trials. This was in line with the ERG's comments for the ipilimumab first-line NICE submission.[3] Therefore, the results of this network meta-analysis were only considered as part of sensitivity analyses.

5.3.2 Estimation of the proportion of patients by health state derived from the clinical data

The partitioned-survival model was developed by fitting survival curves to trial data for PFS and OS. The area underneath the OS curve represented the proportion of patients that were still alive at different points in time, while the proportion of patients in the pre-progression state was identified by the patients located underneath the PFS curve. The area between OS and PFS represented the proportion of post-progression patients, i.e. those who were in the 'post progression' health state. More detailed information on the approach implemented is provided below, in section 5.3.3.

5.3.3 Extrapolation

Standard parametric curve fitting of the PFS and OS data derived from the KEYNOTE-006 trial was initially considered for the extrapolation of the pembrolizumab and ipilimumab data in the long term. The survival curve fitting was carried out in line with the NICE DSU guidelines.[103] All standard parametric models (i.e. exponential, Weibull, Gompertz, log-logistic and log-normal) were considered and compared. The fit of the alternative models was assessed both by considering internal and external validity (i.e. how well they fitted the observed data) and the plausibility of the extrapolated results, respectively.

For pembrolizumab and ipilimumab the estimation of PFS and OS in the short term (up to 1 year) was based on data from the KEYNOTE-006 trial. For PFS KM data up to week 13 was used, followed by parametric curves fitted to the data up to 1 year. For OS, the KM data up to 1 year was utilised. PFS was derived from the IRO assessment since this reflected the primary endpoint data from KEYNOTE-006. Therefore, the effect of 'tumour flare' (i.e. initial evidence of disease progression among clinically stable patients; see Appendix 1), which will lead to longer post-progression survival, has not been incorporated.

PFS and OS estimates for pembrolizumab and ipilimumab were assumed to be applicable across all patients independent of their BRAF status. This was justified on the basis that $BRAF^{V600}$ status did not seem to affect the benefit of pembrolizumab over ipilimumab.[18]

Digitised curves from the most up-to-date published KM data from the BRIM-3[8;101] and the BREAK-3 trials[30;96] were used for estimation of the PFS and OS for vemurafenib and dabrafenib. An alternative option for dabrafenib was to assume equal efficacy with vemurafenib in terms of PFS and OS, consistent with the assumptions made in TA319[3] and the conclusions drawn by the committee for TA321.[17]

A summary of the potential options of PFS and OS projections that can be used in the model for each treatment is presented in Table 70. The table identifies the scenario selected as the base case, which reflects the best available evidence. Fifteen additional scenarios are presented, on the basis of the additional available evidence, which were tested as part of sensitivity analyses. A more detailed discussion of these extrapolation approaches is presented below.

PFS

- ***For all patients ($BRAF^{V600}$ wild type and $BRAF^{V600}$ mutation positive patients)***

In KEYNOTE-006 the first radiological tumour response assessment was performed in week 12. This resulted in a protocol-driven drop of PFS between weeks 12 and 13, and made it challenging to fit the standard parametric curves to the pembrolizumab and ipilimumab PFS data in order to extrapolate beyond the trial period (see Appendix 19). Therefore, a two-part curve fit was applied to the PFS data to account for this. KM curves for pembrolizumab and ipilimumab were used until week 13 and then a parametric curve fit was used beyond this time point.

The assumption of proportional hazards was tested using the Schodefeld residual test. The test result (p = 0. 11) does not rule out using the proportional hazard ratio assumption. The proportional hazard assumption could not be rejected based on a visual inspection of the two-residual plot (see Figure 24 below, and Figures 34, 40 and 49 in Appendix 12). Therefore, a pooled model was used based upon the pembrolizumab and ipilimumab arms included in the KEYNOTE-006 clinical trial for the projection of the PFS using a 2-part extrapolation.

Figure 23. Cumulative hazard plot for PFS from KEYNOTE-006

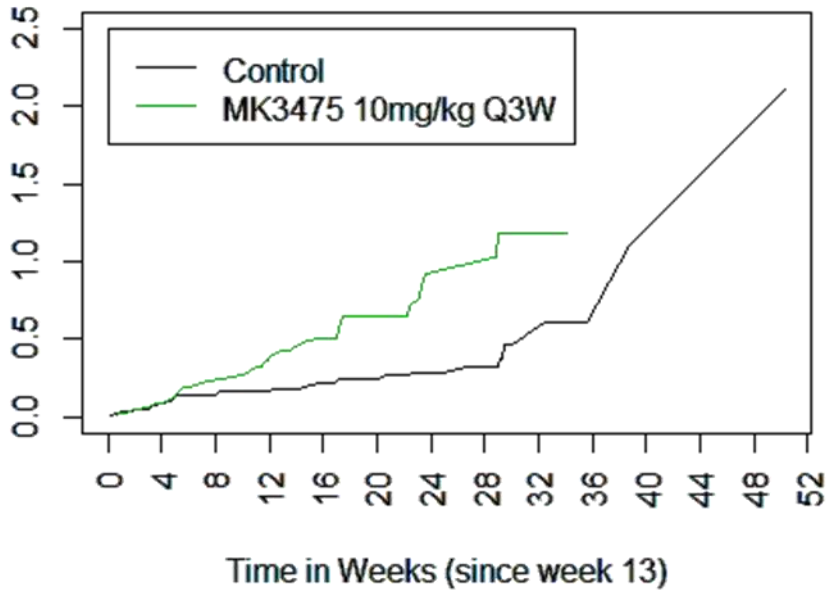


Figure 24. Two-residual plot for pembrolizumab 10mg/kg Q3W PFS from KEYNOTE-006

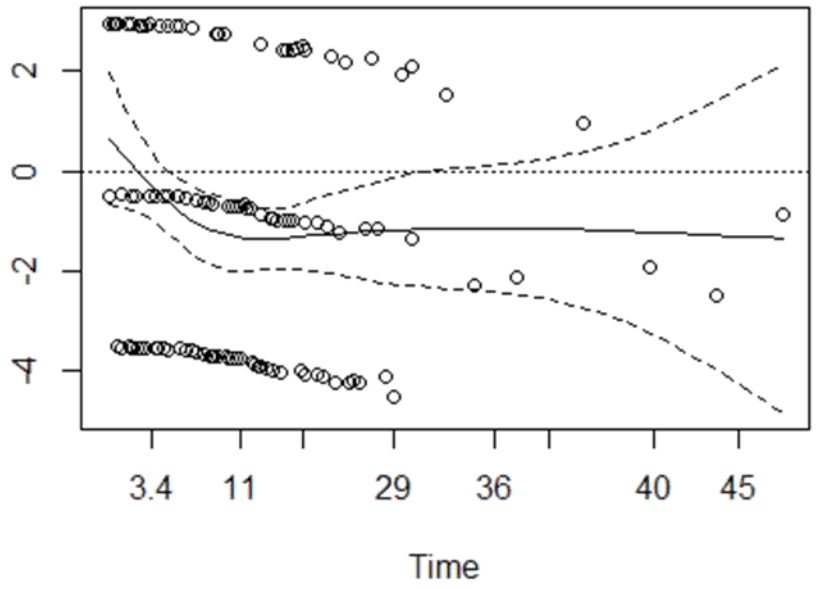


Table 68 reports the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) for the second part of the PFS two-part curve fit for pembrolizumab and ipilimumab based on KEYNOTE-006 PFS data. According to both the AIC and the BIC criteria, Gompertz was the best fit to the PFS data when assuming proportional hazards.

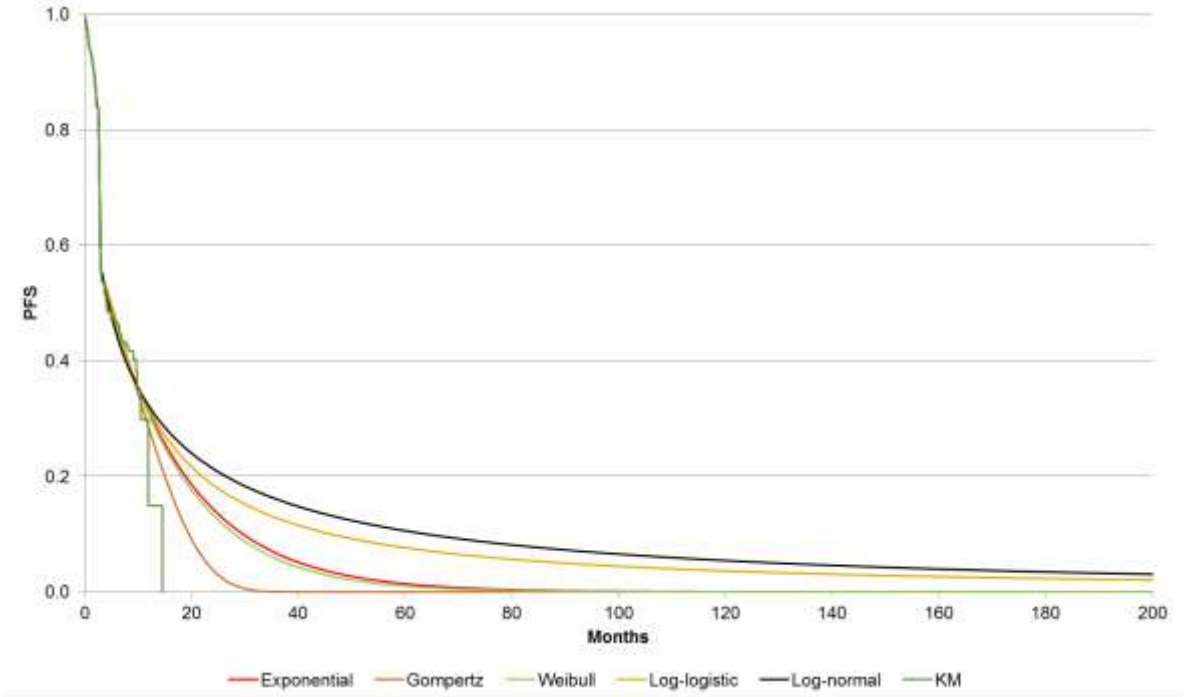
Table 68: AIC and BIC for PFS curve fit for week 13+

	Model for pembrolizumab and ipilimumab for week 13+ (used in the 2-part extrapolation)	
Model	**AIC**	**BIC**
Exponential	803.0	802.5
Weibull	805.0	808.0
LogNormal	810.1	813.1
LogLogistic	807.2	810.2
Gompertz	**788.3**	**793.4**

AIC: Akaike information criterion. BIC: Bayesian information criterion

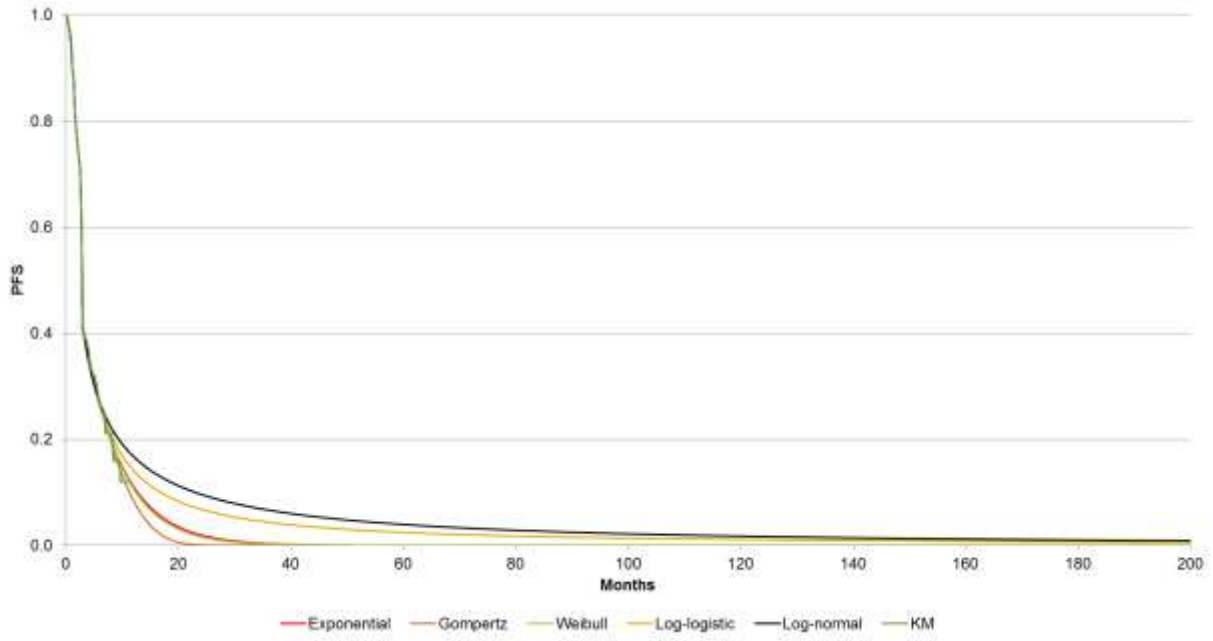
The curve fits for pembrolizumab and ipilimumab are presented in Figure 25. Following visual inspection of the curves, Gompertz was selected to be the best fitting curve for pembrolizumab and ipilimumab PFS due to its AIC and BIC values. As previously mentioned (see section 5.3.2), using PFS based on the IRO assessment may overestimate post-progression survival; therefore, it may not fully capture the impact of treatment.

Figure 25: PFS KM data until week 12 followed by standard parametric curve fitting from week 13 onwards in the pembrolizumab arm



Key: KM, Kaplan-Meier; OS, overall survival.

Figure 26: PFS KM data until week 12 followed by standard parametric curve fitting from week 13 onwards in the ipilimumab arm



Key: *KM, Kaplan-Meier; OS, overall survival.*

Approaches followed to extrapolate pembrolizumab PFS in the long-term:

1) Using the parametric curve fit to PFS KEYNOTE-006 data

PFS for pembrolizumab was modelled using KM data from the KEYNOTE-006 trial until Week 13. PFS was then extrapolated using the Gompertz curve estimated from the pooled model as described above.

2) Using output from the network meta-analysis

The network meta-analysis described in section 4.10 was used to model PFS in scenario analyses. Three different models (each with a different network of evidence) were used to provide alternative PFS curves.

Approaches followed to extrapolate ipilimumab PFS in the long-term

1) Using the ipilimumab KM data until week 13 and the parametric curve fit to PFS KEYNOTE-006 data afterwards

Under this modelled extrapolation scenario, PFS for ipilimumab was modelled using KM data from the KEYNOTE-006 trial until Week 13. PFS was then extrapolated using the Gompertz curve estimated from the pooled model as described above. This was the base case included in the model.

2) **Using the KN-006 K-M data until Week 13, followed by the PFS HR from KEYNOTE-006 applied to the pembrolizumab curve fit**

Under this modelled extrapolation scenario, PFS for ipilimumab was modelled using KM data from the KEYNOTE-006 trial until Week 13. PFS was then extrapolated by applying the PFS HR estimated from KEYNOTE-006 to the standard parametric curve that fitted best the pembrolizumab PFS data.

3) **Using output from the network meta-analysis**

The network meta-analysis described in section 4.10 was used to model PFS in scenario analyses. Three different models (each with a different network of evidence) were used to provide alternative PFS curves.

- ***For BRAF^{V600} mutation positive patients***

Approach followed to extrapolate vemurafenib PFS in the long-term:

1) **Using KM data from McArthur (2014)[8] followed by a monthly risk of progression[3]**

Under this modelled scenario, the PFS KM data published by McArthur et al. (2014)[8] was applied up to week 39. Afterwards, the monthly risk of progression reported in TA319 was implemented.[3]

2) **Using output from the network meta-analysis**

The network meta-analysis described in section 4.10 was used to model PFS in scenario analyses. Three different models (each with a different network of evidence) were used to provide alternative PFS curves.

Approaches followed to extrapolate dabrafenib PFS in the long-term

1) **Using KM data from Hauschild et al. (2012),[30] followed by a monthly risk of progression**

Under this modelled scenario, the KM data published by Hauschild et al. (2014)[30] was used up to week 39. Afterwards, the monthly risk of progression reported in TA319 was used.[3] This was the base case included in the model.

2) **Assuming equal efficacy with vemurafenib**

Under this modelled extrapolation scenario, a similar effect in PFS was assumed for dabrafenib and vemurafenib, using vemurafenib data. This was based on TA319[3] where the committee agreed that dabrafenib and vemurafenib were unlikely to differ in clinical effectiveness and that it would not be unreasonable to assume that they have similar effect.

3) **Using output from the network meta-analysis**

The network meta-analysis described in section 4.10 was used to model PFS in scenario analyses. Three different models (each with a different network of evidence) were used to provide alternative PFS curves.

OS

- ***For all patients ($BRAF^{V600}$ wild type and $BRAF^{V600}$ mutation positive patients)***

When the Schodefeld residual test was implemented to OS data from KEYNOTE-006, the assumption of proportional hazards could not be ruled out (p = 0. 279). Additionally, the proportional hazard assumption could neither be rejected based on a visual inspection of the two-residual plot (see Figure 28 below, and Figures 31, 37, 43 and 46 in Appendix 12). The confidence bands were considerably wide and potential turning points around weeks 10 and 45 could not be confirmed. Therefore, a pooled model was used for the pembrolizumab 10mg/kg Q3W and the ipilimumab arms included in the KEYNOTE-006 clinical trial for the projection of the OS.

Figure 27. Cumulative hazard plot for OS from KEYNOTE-006

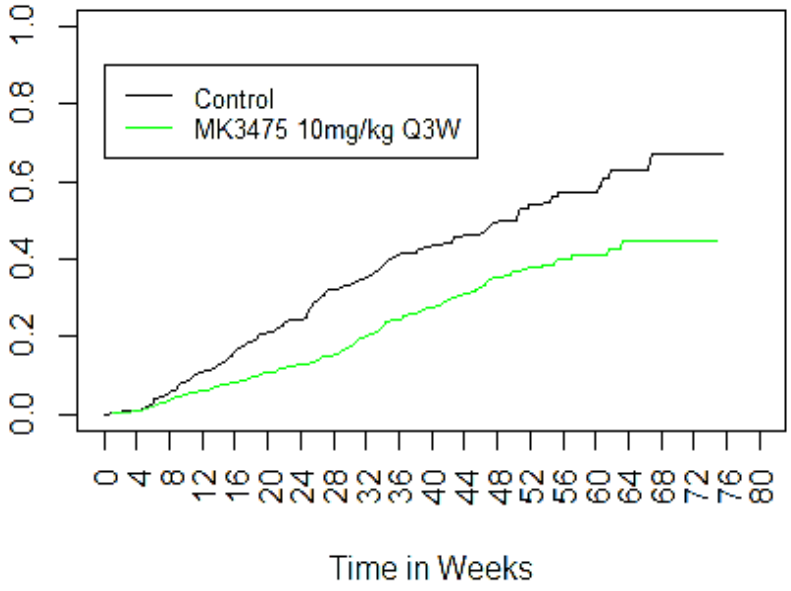


Figure 28. Two-residual plot for pembrolizumab 10mg/kg Q3W OS from KEYNOTE-006

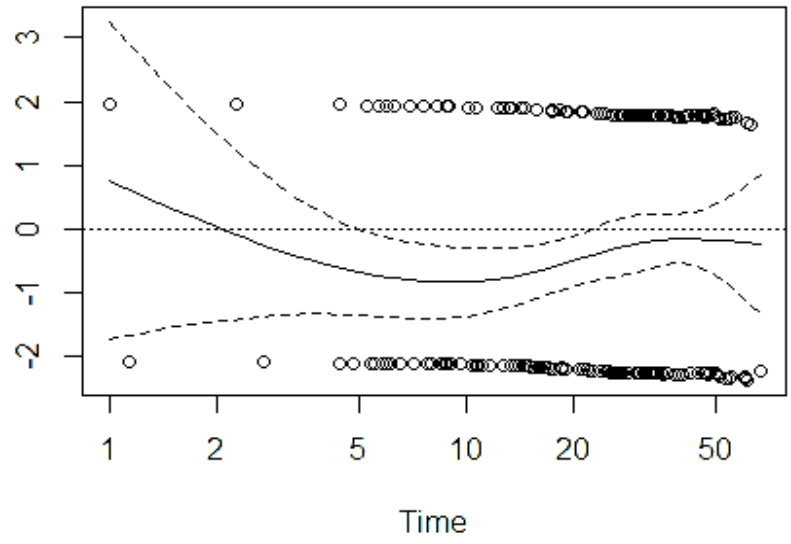


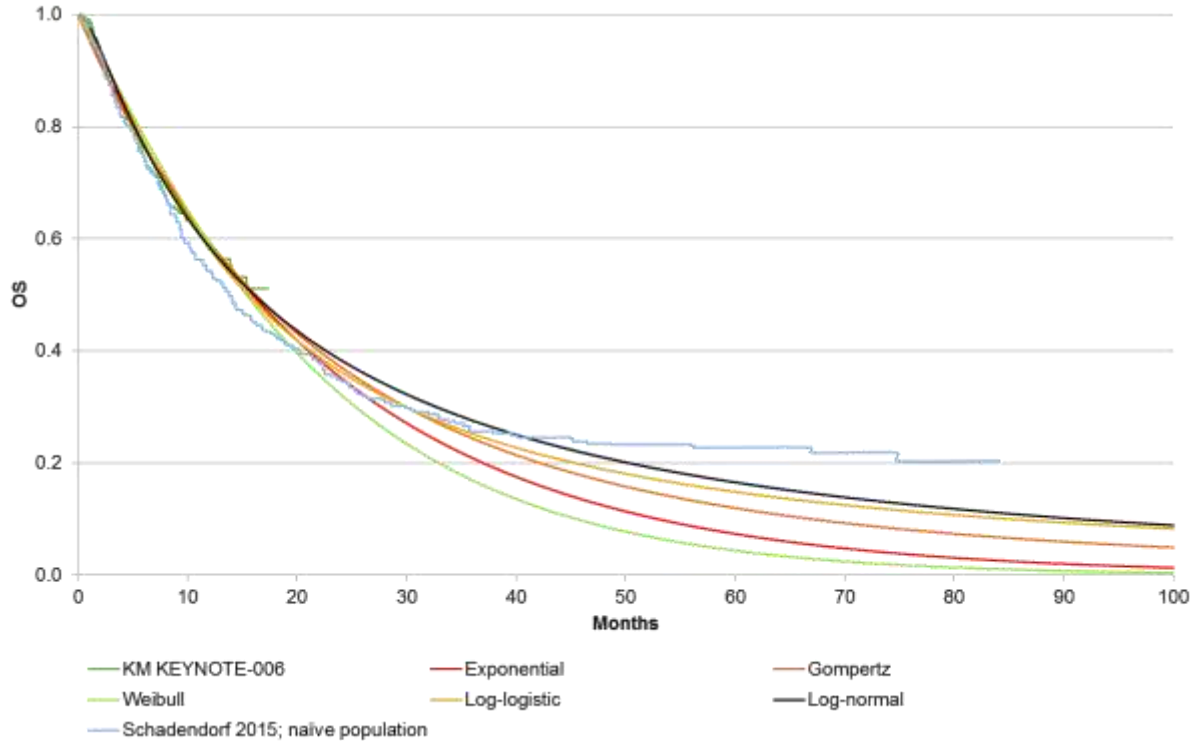
Table 69: AIC and BIC for OS curve fit

	Model for pembrolizumab and ipilimumab for week 13+ (used in the 2-part extrapolation)	
Model	**AIC**	**BIC**
Exponential	2371	2371
Weibull	2368	2373
LogNormal	**2358**	**2362**
LogLogistic	2362	2367
Gompertz	2363	2370

AIC: Akaike information criterion. BIC: Bayesian information criterion

Figure 29 presents the parametric curves fitted for ipilimumab OS data compared to the long-term data for ipilimumab presented by Schadendorf (2015).[9]

Figure 29: Comparison of the projected ipilimumab OS based on the standard parametric curve fitting compared to data from KEYNOTE-006 and Schadendorf (2015)



Key: *KM, Kaplan-Meier; OS, overall survival.*

Based on the previous figure, the standard parametric curve fitting resulted in survival estimates that were mostly not clinically plausible in the long term, as long-term survival for ipilimumab was projected below what would be expected with ipilimumab based on published data.[9] This was expected since the findings from the previous submissions for ipilimumab, both administered as first- and a second-line treatment, and the ongoing submission for pembrolizumab in patients previously treated with ipilimumab[22] encountered the same issue. In these submissions the 'best-fit' standard parametric curves did not fit the KM data particularly well and the approach was considered to be inappropriate to project OS for immunotherapies in the long term.[2;3] Therefore, it was deemed inappropriate to use a standard parametric curve fit based only upon within trial data. Consequently, alternative methods to the standard parametric curve fit were considered to extrapolate survival beyond the trial period. A summary of all the options considered either in the base case or in sensitivity analyses is presented in Table 70. A more detailed discussion is presented below.

Approaches followed to extrapolate pembrolizumab OS in the long-term

1) **Using the KM data from KEYNOTE-006 followed by the ipilimumab long-term survival curve for treatment-naïve patients from Schadendorf (2015)[9] (assuming the same conditional relative rates of survival: base case)**

The results of the KEYNOTE-006 trial demonstrated that pembrolizumab resulted in significant improvement in OS (see Section 4.7).[18] Since pembrolizumab is an immunotherapy like ipilimumab, it is expected that it would have a similar survival profile in the long-term.[9]

Under this modelled extrapolation scenario, OS for pembrolizumab was modelled using KM data from the KEYNOTE-006 trial until 1 year. OS was then extrapolated by assuming the same conditional survival rates as those observed for ipilimumab among treatment-naïve patients using data digitised from Schadendorf *et al*.[9] Data for treatment naïve patients was available from Schadendorf *et al*. (2015)[9] for 7 years. From the end of Year 7 registry data from Balch *et al*. (2001)[88] was utilised. Based on the proportion of patients in these stages in the KEYNOTE-006 trial, the stage IIIC and the stage IV data from the registry data were combined, following the approach previously implemented in TA319. [3] The registry data only reported melanoma specific mortality; therefore, background survival was applied in addition.[104] This was the base case included in the model.

An implicit assumption under this extrapolation scenario was that all patients surviving until 1 year in the pembrolizumab trial had the same future survival prospects (i.e. conditional survival probability) as that seen in the ipilimumab trials for treatment naïve patients. Clinical data indicates that a larger proportion of patients can be expected to survive in the longer term with pembrolizumab.

2) **Using the ipilimumab long-term survival curve for the combined population of treatment-naïve and previously treated patients from Schadendorf (2015)[9] (assuming the same conditional relative rates of survival)**

Under this modelled extrapolation scenario, OS for pembrolizumab was modelled using KM data from the KEYNOTE-006 trial until year 1. OS was then extrapolated by assuming the same conditional survival rates as those observed for ipilimumab among the combined population of treatment-naïve and treatment experienced patients using data from the primary analysis of Schadendorf *et al*.[9] Data for the combined population of treatment naïve and treatment experienced patients was available from Schadendorf *et al*. (2015) for 10 years.[9] From the end of year 10 registry data from Balch *et al*. (2001)[88] was utilised (in a

similar fashion as for the previous extrapolation scenario), and background survival data was applied in addition.[104]

3) **Using the OS HR for pembrolizumab vs. ipilimumab from the KEYNOTE-006 trial on the treatment-naïve population from Schadendorf (2015)[9] (assuming the same conditional relative rates of survival)**

Under this modelled extrapolation scenario, OS for pembrolizumab was modelled using KM data observed for ipilimumab among treatment-naïve patients using digitised data from Schadendorf et al. [9] A hazard ratio of 0.69 was reported in the KEYNOTE-006 trial for the difference in OS between pembrolizumab and ipilimumab.[18] This was utilised to adjust the observed ipilimumab OS data from Schadendorf et al. (2015) to the OS that would have been expected with pembrolizumab. An implicit assumption under this extrapolation scenario was that the assumption of proportional hazards holds between pembrolizumab and ipilimumab. This assumption is justified based on the analysis of proportional hazards presented above for the KEYNOTE-006 trial data. Data for the population of treatment naïve patients was available from Schadendorf *et al*. (2015) for 7 years.[9] From the end of year 7 registry data from Balch *et al*. (2001)[88] was utilised (in a similar fashion as for the previous extrapolation scenarios), and background survival data was applied in addition.[104]

4) **Using the OS HR for pembrolizumab vs. ipilimumab from the KEYNOTE-006 trial on the combined population of treatment-naïve and previously treated patients from Schadendorf (2015)[9] (assuming the same conditional relative rates of survival)**

Under this modelled extrapolation scenario, OS for pembrolizumab was modelled using KM data observed for ipilimumab among the combined population of treatment-naïve and treatment experienced patients using data digitised from the primary analysis of Schadendorf *et al*.[9] A hazard ratio of 0.69 (reflecting the results of the KEYNOTE-006 trial) was applied to this data.[18] This was utilised to adjust the observed ipilimumab OS data from Schadendorf *et al*. (2015)[9] to the OS that would have been expected with pembrolizumab.

Data for the combined population of treatment naïve and treatment experienced patients was available from Schadendorf *et al*. (2015) for 10 years.[9] From the end of Year 10 registry data from Balch *et al*. (2001)[88] in combination with background survival[104] were used. For the implementation of this extrapolation scenario we assumed proportional hazards between

pembrolizumab and ipilimumab, as indicated by the results of the analysis of proportional hazards presented above for the KEYNOTE-006 trial data.[88]

5) **Using the parametric curve fit to OS KEYNOTE-006 data**

Under this modelled extrapolation scenario, OS was modelled using the log-normal curve estimated from the pooled model as described above as this was the modelled curve which best fit the data based on the AIC and BIC.

6) **Using output from the network meta-analysis**

The network meta-analysis described in section 4.10 was used to model OS in scenario analyses. Four different models (each with a different network of evidence) were used to provide alternative OS curves.

Approaches followed to extrapolate ipilimumab OS in the long-term

1) **Using the ipilimumab long-term survival curve for treatment-naïve patients from Schadendorf (2015)[9]**

Under this modelled extrapolation scenario, OS for ipilimumab was modelled using KM data from the KEYNOTE-006 trial until year 1. OS was then extrapolated by assuming the conditional survival observed among treatment-naïve patients using data from Schadendorf *et al*.[9] Data for treatment naïve patients was available from Schadendorf *et al*. (2015) for 7 years.[9] From the end of year 7 registry data from Balch *et al*. (2001)[88] was utilised to reflect melanoma-specific mortality following the approach previously implemented in TA319.[3] This was combined with background survival data.[104] This was the base case included in the model.

2) **Using the ipilimumab long-term survival curve for the combined population of treatment-naïve and previously treated patients from Schadendorf (2015)[9]**

Under this modelled extrapolation scenario, OS KM data from the KEYNOTE-006 trial for ipilimumab was used until year 1. Afterwards, the conditional survival rates observed among the combined population of treatment-naïve and treatment experienced patients from the primary analysis of Schadendorf *et al* were used.[9] Data for the combined population of treatment naïve and treatment experienced patients was available from Schadendorf *et al*. (2015) for 10 years. From the end of Year 10 registry data from Balch *et al*. (2001)[3;88] was combined with background survival data.[104]

3) **Using the treatment-naïve population from Schadendorf (2015)[9]**

Under this modelled extrapolation scenario, OS for ipilimumab was modelled using digitised data for treatment naïve patients from Schadendorf *et al*.[9] This data was available for 7 years. Afterwards, registry data from Balch *et al*. (2001)[3;88] combined with background survival estimates[104] were used.

4) **Using the combined population of treatment-naïve and previously treated patients from Schadendorf (2015)[9]**

In this modelled extrapolation scenario, OS for ipilimumab was modelled using data digitised from the combined population of treatment naïve and treatment experienced patients presented in Schadendorf *et al*.[9] Data was available for 10 years. Afterwards, registry data from Balch *et al*. (2001)[3;88] combined with background survival data were applied.[104]

5) **Using the parametric curve fit to OS KEYNOTE-006 data**

Under this modelled extrapolation scenario, OS was modelled using the log-normal curve estimated from the pooled model as described above as this was the modelled curve which best fit the data based on the AIC and BIC.

6) **Using the OS HR from KEYNOTE-006 applied to the pembrolizumab curve fit**

Under this modelled extrapolation scenario, OS for ipilimumab was modelled by applying the OS HR estimated from KEYNOTE-006 to the standard parametric curve that fitted best the pembrolizumab OS data (log-normal).

7) **Using output from the network meta-analysis**

The network meta-analysis described in section 4.10 was used to model OS in scenario analyses. Four different models (each with a different network of evidence) were used to provide alternative OS curves.

- ***For BRAF^{V600} mutation positive patients***

Approaches followed to extrapolate vemurafenib OS in the long-term:

1) **Using the vemurafenib projections presented as part of TA319 [3]**

Under this modelled extrapolation scenario, OS for vemurafenib was modelled using digitised KM data from the BRIM-3 trial until Week 60.[101] OS was then extrapolated in line

with the assumptions used in TA319.[3] This extrapolation included three different monthly risks of death between weeks 61 and 100 (0.0658), weeks 101 and 152 (0.0328) and weeks 153 and 200 (0.0141). Following this, registry data from Balch *et al*. (2001)[88] was utilised, with a separate curve fit to data between years 4 and 5, and year 5 onwards, consistent with TA319. Additionally, background survival[104] was applied since the registry data only reported melanoma-specific mortality.

2) Using output from the network meta-analysis

The network meta-analysis described in section 4.10 was used to model OS in scenario analyses. Four different models (each with a different network of evidence) were used to provide alternative OS curves.

Approaches followed to extrapolate dabrafenib OS in the long-term

1) Using the vemurafenib projections presented as part of TA319[3]

Under this modelled extrapolation scenario, OS for dabrafenib was modelled using digitised KM data from the BREAK-3 trial until Week 60.[96] OS was then extrapolated consistent with the extrapolation described for vemurafenib, in line with the assumption made in TA319 of similar efficacy between vemurafenib and dabrafenib[3] This was the base case included in the model.

2) Assuming equal efficacy with vemurafenib

Under this modelled extrapolation scenario, OS for dabrafenib was modelled as identical to OS for vemurafenib. This is in line with the assumption made in TA319[3] and justified as part of the NICE guidance for dabrafenib (TA321), whereby the Committee accepted as reasonable to assume a similar effect between vemurafenib and dabrafenib.[17]

3) Using output from the network meta-analysis

The network meta-analysis described in section 4.10 was used to model OS in scenario analyses. Four different models (each with a different network of evidence) were used to provide alternative OS curves.

Selected base case scenario:

The base case selected for the analysis is presented in Table 70. This table also presents other possible combinations of PFS and OS that were considered in the model. The base case scenario was selected to maximise the use of the PFS and OS data derived from the

KEYNOTE-006 trial for both pembrolizumab and ipilimumab from the available follow-up period. The standard parametric OS fitted curves resulted in clinically implausible estimations. This was expected as previous submissions have encountered the same issue with immune-oncology therapies.[2;3;22] Therefore, we selected the extrapolation scenario based on the long-term analyses for ipilimumab[9] as the most appropriate base case scenario since it reflected the most robust, longest follow-up data available for an immuno-therapy. Additionally, this extrapolation scenario was consistent with the base case selected in the ongoing NICE appraisal of pembrolizumab for patients previously treated with ipilimumab (ID760).[22]

In the selected base case scenario, data from the treatment-naïve cohort was used since it more closely reflected the relevant population of the model. Extrapolation based on the combined population of treatment-naïve and previously treated patients from the analysis by Schadendorf et al. [9] was considered in sensitivity analyses.

Table 70: Summary of extrapolation options for pembrolizumab and comparator arms

	For all patients (BRAF^{V600} mutation-positive and BRAF^{V600} mutation negative patients)		For patients with BRAF^{V600} positive mutations	
	Pembrolizumab	**Ipilimumab**	**Vemurafenib**	**Dabrafenib***
Base Case	**PFS**: KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** KM data from KEYNOTE-006, followed by Schadendorf naïve population (to 7 years), followed by Balch (2001) registry data	**PFS:** KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** KM data from KEYNOTE-006, followed by Schadendorf naïve population (to 7 years), followed by Balch (2001) registry data	**PFS:** KM data from McArthur et al. (2014), followed by monthly risk of progression week 39+ **OS:** digitised KM data from BRIM-3 trial until week 60, followed by three different monthly risks of death between weeks 61 and 100, weeks 101 and 152, and weeks 153 and 200 (TA319), followed by Balch (2001) registry data	**PFS:** KM data from Hauschild et al. (2012), followed by monthly risk of progression week 39+ **OS:** digitised KM data from BREAK-3 trial until week 60, followed by extrapolation similar to vemurafenib, i.e. three different monthly risks of death between weeks 61 and 100, weeks 101 and 152, and weeks 153 and 200 (TA319), followed by Balch (2001) registry data
Scenario 1		**PFS:** KEYNOTE-006 KM data to week 13, followed by HR applied to pembrolizumab curve fit **OS:** KM data from KEYNOTE-006, followed by Schadendorf naïve population (to 7 years), followed by Balch (2001) registry data		
Scenario 2	**PFS:** KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** KM data from KEYNOTE-006, followed by Schadendorf combined population (to 10 years), followed by Balch (2001) registry data	**PFS:** KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** KM data from KEYNOTE-006, followed by Schadendorf combined population (to 10 years), followed by Balch (2001) registry data		
Scenario 3		**PFS:** KEYNOTE-006 KM data to week 13, followed by HR applied to pembrolizumab curve fit **OS:** KM data from KEYNOTE-006, followed by Schadendorf combined population (to 10 years), followed by Balch (2001) registry data		
Scenario 4	**PFS:** KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** HR applied to Schadendorf naïve population (to 7 years), followed by Balch (2001) registry data	**PFS:** KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** Schadendorf naïve population (to 7 years), followed by Balch (2001) registry data		
Scenario 5		**PFS:** KEYNOTE-006 KM data to week 13, followed by HR applied to pembrolizumab curve fit **OS:** Schadendorf naïve population (to 7 years), followed by Balch (2001) registry data		

	For all patients (BRAF^{V600} mutation-positive and BRAF^{V600} mutation negative patients)		For patients with BRAF^{V600} positive mutations	
	Pembrolizumab	**Ipilimumab**	**Vemurafenib**	**Dabrafenib***
Scenario 6	**PFS:** KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** HR applied to Schadendorf combined population (to 10 years), followed by Balch (2001) registry data	**PFS:** KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** Schadendorf combined population (to 10 years), followed by Balch (2001) registry data		
Scenario 7		**PFS:** KEYNOTE-006 KM data to week 13, followed by HR applied to pembrolizumab curve fit **OS:** Schadendorf combined population (to 10 years), followed by Balch (2001) registry data		
Scenario 8	**PFS**: KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** Standard parametric curve fit	**PFS:** KEYNOTE-006 KM data to week 13, followed by curve fit **OS**: Standard parametric curve fit		
Scenario 9		PFS: KEYNOTE-006 KM data to week 13, followed by HR applied to pembrolizumab curve fit **OS**: Standard parametric curve fit		
Scenario 10		**PFS**: KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** HR applied to pembrolizumab curve fit		
Scenario 11		**PFS:** KEYNOTE-006 KM data to week 13, followed by HR applied to pembrolizumab curve fit **OS:** HR applied to pembrolizumab curve fit		
Scenario 12	PFS & OS: NMA, NMA scenario 1	PFS & OS: NMA, NMA scenario 1	PFS & OS: NMA, NMA scenario 1	PFS & OS: NMA, NMA scenario 1
Scenario 13	PFS & OS: NMA, NMA scenario 2	PFS & OS: NMA, NMA scenario 2	PFS & OS: NMA, NMA scenario 2	PFS & OS: NMA, NMA scenario 2
Scenario 14	PFS: KEYNOTE-006 KM data to week 13, followed by curve fit OS: NMA, NMA scenario 3a	PFS: KEYNOTE-006 KM data to week 13, followed by curve fit OS: NMA, NMA scenario 3a	PFS: K-M data from McArthur et al. (2014), followed by monthly risk of progression Week 39+ OS: NMA, NMA scenario 3a	PFS: K-M data from Hauschild et al. (2012), followed by monthly risk of progression Week 39+ OS: NMA, NMA scenario 3a
Scenario 15	PFS & OS: NMA, NMA scenario 3b	PFS & OS: NMA, NMA scenario 3b	PFS & OS: NMA, NMA scenario 3b	PFS & OS: NMA, NMA scenario 3b
Scenario 16	**PFS**: KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** KM data from KEYNOTE-006, followed by Schadendorf naïve population (to 7 years), followed by Balch (2001) registry data	**PFS:** KEYNOTE-006 KM data to week 13, followed by curve fit **OS:** KM data from KEYNOTE-006, followed by Schadendorf naïve population (to 7 years), followed by Balch (2001) registry data	**PFS:** KM data from McArthur et al. (2014), followed by monthly risk of progression week 39+ **OS:** digitised KM data from BRIM-3 trial until week 60, followed by three different monthly risks of death between	PFS & OS: Equal to vemurafenib

	For all patients ($BRAF^{V600}$ mutation-positive and $BRAF^{V600}$ mutation negative patients)		For patients with $BRAF^{V600}$ positive mutations	
	Pembrolizumab	Ipilimumab	Vemurafenib	Dabrafenib*
			weeks 61 and 100, weeks 101 and 152, and weeks 153 and 200 (TA319), followed by Balch (2001) registry data	

Key: HR, hazard ratio; KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; TA, technology appraisal.

5.3.4 Input from clinical experts

The general model structure is consistent with the model used to assess the cost-effectiveness of pembrolizumab in patients previously treated with ipilimumab, for which a NICE STA is currently ongoing.[22]

In terms of the benefit of pembrolizumab compared to ipilimumab, the clinicians consulted stated that the results of KEYNOTE-006 conformed to their understanding of the new PD-1 checkpoint inhibitors.[18]

5.4 Measurement and valuation of health effects

The burden of metastatic melanoma from the patient perspective has been evaluated in several clinical trials.[52] The immediate period following diagnosis was often associated with high levels of HRQoL impairment. Patients report experiencing more pain, less energy and more interference of social activities. Acute survival is followed by extended survival, which is dominated more by fears of recurrence and less by the physical limitations of the cancer.[52] The most common patient-reported, HRQoL impairments are elevated pain and fatigue.[105]

Treatment related toxicities can also have an impact on quality of life with symptoms such as diarrhoea, nausea, stomatitis, hair loss and flu-like syndrome being associated with many treatments given for advanced melanoma.[106]

HRQoL is often similar to the expected quality of life of members of the general population until the months immediately prior to end of life.[107-110]

A patient's utility would be expected to increase or remain the same if the patient survives in the long-term due to clinical improvement.[52;108-110] For patients who do not become long-term survivors quality of life has been shown to decrease with a large reduction in patient quality of life seen in the month prior to death.[108-110]

5.4.1 Health-related quality-of-life data from clinical trials

The only trial assessing pembrolizumab in patients who are naïve to treatment with ipilimumab and evaluating HRQoL was the KEYNOTE-006 trial. Therefore, all trial-based HRQoL analyses conducted for the purpose of the economic section were derived from this trial.

Method of elicitation/Method of valuation/Point when measurements were made/Consistency with reference case/Appropriateness for cost-effectiveness analysis/Results with confidence intervals

In the randomised phase III study (KEYNOTE-006), changes from baseline in the HRQoL in patients who are naïve to treatment with ipilimumab were compared to those from patients treated with ipilimumab. Patient reported outcomes, measured with EQ-5D and European Organisation for Research and Treatment Cancer Quality of Life Questionnaire (EORTC QLQ-C30), were assessed at the following time points: baseline-cycle 1 (week 0), cycle 2 (week 3), cycle 3 (week 6), cycle 5 (week 12), cycle 9 (week 24); cycle 13 (week 36), end of treatment; safety follow up (approximately 30 days after the last dose of study drug or before the initiation of a new antineoplastic treatment, whichever comes first).

EQ-5D is the most common generic preference-based measure (PBM).[111] Evaluation of HRQoL using EQ-5D directly from patients is consistent with NICE reference case and is used in the cost-effectiveness model.[112]

The EORTC QLQ-C30 is a condition specific-measure and is one of the most commonly used in cancer. However it cannot be used directly in economic evaluation as it does not incorporate preferences and would need to be converted using an algorithm.[111] EQ-5D data have been derived from the KEYNOTE-006 clinical trial; therefore, there was no need to map the EORTC QLQ-C30 values collected in the KEYNOTE-006 to EQ-5D.

The PRO analyses are based on the FAS population. Results for EQ-5D questionnaires reported below were based on the first interim analysis of KEYNOTE-006 (data cutoff date: 3rd September 2014). Results are presented across this section for pembrolizumab 10mg/kg Q3W (and dosage relevant to this submission) versus ipilimumab. The EORTC QLQ-C30 results are not currently available (see section 4.7).

EQ5D:

Data was collected in the KEYNOTE-006 trial (i.e. at IA1) but was not all the data was reported in the database at time of EQ-5D analyses performed. The proportion of missing reported EQ-5D data is reported in Table 71. Therefore, only complete case analyses were used to assess HRQoL.

Table 71: Compliance of EQ-5D

	Non-missing records/Total records (%)		
	MK-3475		Control
	10 mg Q2W	10 mg Q3W	
Baseline	230/278 (82.73)	223/277 (80.51)	202/256 (78.91)
Primary Analysis*	881/1163 (75.75)	790/1166 (67.75)	363/682 (53.23)

*while patients were on treatment (on or prior to date of last dose) for treated population

Utilities were calculated based upon both time to death and progression-based health states. UK preference-based scores were used for all patients analysed from the KEYNOTE-006 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique (see Appendix 30).[113]

A diagnostic analysis conducted to compare baseline EQ-5D utility scores, collected at the first visit (treatment cycle 1), showed that there was no significant difference in baseline utilities across the two treatment arms.

As mentioned at the beginning of this section, health related quality of life using EQ-5D data was collected at different time points, with only one assessment post-progression.

- Time to death utilities

Clinical opinion has suggested that there is a decline in HRQoL in the final months of life of advanced melanoma patients, which may not be appropriately captured solely through the use of progression-based health state utilities.[110] Therefore, alternative approaches to implementing HRQoL were used in ipilimumab first-line (TA319)[3] NICE submission using time to death utility values. This approach reflects the decline in melanoma patients' quality of life as they approach death. It utilizes more health states and potentially offers better fit.[110;114] This approach was accepted as the most preferable in ipilimumab first-line submission (TA319).[3] The same approach was used in the ongoing NICE submission for pembrolizumab for treating unresectable metastatic melanoma after progression with ipilimumab [ID760].

In the base case scenario, the values used for the time to death utilities in the model were the pooled values from the 10mg/kg Q3W pembrolizumab arm and the ipilimumab arm, as there was no significant difference in quality of life between the two arms.

In line with the methodology accepted in TA319[3] and clinical expectation that prognosis will have the greatest impact on patients quality of life, utility values were calculated based upon time to death with the categories selected derived from those used in TA319[3] . Even though the <30 days category has small patients number it was not grouped to another category as the utility was quite different to those from the other groups. Results are presented in Table 75.

Utility values are seen to decrease when patients are closer to the time of death. The analyses of the intervals related to time to death lower than 360 days focused on patients with observed death dates. The justification to exclude patients whose death dates were

censored was that their EQ-5D values could not be linked to their time-to-death category. However, for the category of 360 or more days to death, patients with censored death date of 360 days or longer were also included since their EQ-5D data related to a survival of at least 360 days, independent of when the death date was censored.

In sensitivity analyses the values reported in TA319 have been used as an alternative source of time to death utility values (Table 72).[3]

Table 72: EQ-5D health utility score analysis based on time to death from TA319[3]

Time to death (days)	Utility	N	SD
≥360	0.89	676	0.112202
[270, 360)	0.87	221	0.115384
[180, 270)	0.85	301	0.130789
[90, 180)	0.81	336	0.131085
[30, 90)	0.74	232	0.153492
<30	0.63	49	0.145942
Key: *N, number; SD, standard deviation.*			

HRQoL has been age-adjusted using the values from Kind et al;[115] as the average age of patients increases (up to the 75+ age band) a utility decrement of 0.0039 (from the age of 60 to 75) is applied per year to reflect the natural decrease in utility associated with increasing age. This decrement was calculated based upon the starting age of patients in the trial and updates as the starting age varies in probabilistic analysis.

- Progression based utilities

Another approach, more commonly seen in previous oncology economic modelling literature, is to define health states based on time relative to disease progression. While this approach generates results to fit the economic model by health state, there is a practical issue with trial-based utility, where the utility data is usually collected up to drug discontinuation or at the 30-day-post-study safety follow-up visit, but no further. Therefore, the utility data for post-progression is very limited as it is usually collected right after progression, thus missing the utility data as patients quality of life deteriorates when getting closer to death. This could lead to an overestimate of the utility in post-progression state. Another limitation to this approach is that progression is usually determined based on some relative change in tumour size from the baseline. However, baseline tumour sizes across studies can vary within a wide range and disease progression can be determined using different criteria within a same study and/or across studies. This makes it difficult to transfer utility results across studies, or even across disease phases.

Utility values were calculated based upon the trial data for both pre-progression and post-progression for both treatment arms (Table 73):

- EQ-5D scores collected at all visits before the progression date were used to estimate utility for the progression-free health state.

- EQ-5D scores collected at all visits after the progression date were used to estimate utility for the progressive state.

The analyses were undertaken following the IRO assessment approach for which the results are reported by both an independent review committee and an oncologist (Table 73).

Based on the KEYNOTE-006 trial, a comparison analysis based on baseline utilities showed that there was no statistical significant difference across treatment groups so the utilities between the ipilimumab and the pembrolizumab 10mg/kg Q3W treatment arms were pooled together (Table 73).

Table 73: EQ-5D health utility score analysis based on progression from KEYNOTE-006 trial (by IRO assessment)

	MK-3475 10 mg Q3wk					Ipilimumab					Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	235	670	0.81	0.01	(0.80, 0.83)	197	471	0.77	0.01	(0.75, 0.80)	432	1141	0.80	0.01	(0.78, 0.81)
Progressed	135	229	0.71	0.02	(0.67, 0.75)	137	191	0.68	0.02	(0.63, 0.73)	272	420	0.70	0.02	(0.67, 0.73)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included

As in previous melanoma trials, it can be seen that there was not a large difference between pre- and post-progression utilities, indicating that progression status alone is unlikely to be sufficiently reflective of changes in quality of life. Utilities based upon time to death from the trial showed much more substantial changes with reduced life expectancy, more in line with clinical expectation.

Progression-based utility values from the KEYNOTE-006 trial were used in sensitivity analysis (i.e. 0.80 for those in the pre-progression health state and 0.70 for those who have progressed). An alternative source for progression-based utilities was also considered in sensitivity analysis; those reported by Batty *et al*. (2011)[114] (0.80 pre-progression and 0.76 post-progression).

5.4.2 Mapping

Not applicable as HRQoL was derived from the KEYNOTE-006 EQ-5D data.

Utilities were evaluated using EQ-5D directly from patients from the KEYNOTE-006 trial, which is consistent with the NICE reference case.

5.4.3 Systematic searches for relevant HRQoL data

The relevant HRQoL data from the published literature and from unpublished data were identified through a systematic literature search carried out during the period between 16 July 2014 and 23 July 2014, and updated in March 2015 for advanced melanoma (see Appendix 21 for more details).

As previously described in section 5.1, the second research questions posed in accordance with the decision problem was the assessment of HRQoL (in terms of utilities) associated with advanced melanoma.

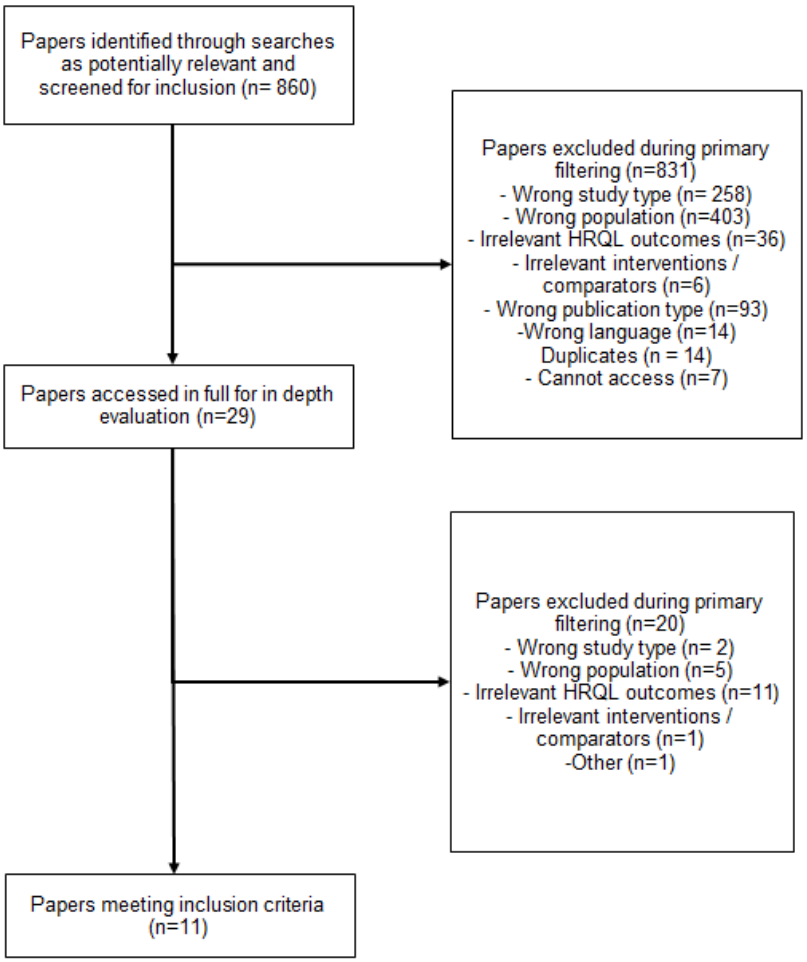
A comprehensive literature search relative to this research questions was carried out using the different databases presented in section 5.1: MEDLINE and MEDLINE In-process (using Ovid platform); EconLit; EMBASE; The Cochrane Library, including the following NHS EED and HTA database.

Hand searches were also performed, constrained to the most recent 2 years, and focusing on the following conferences: ASCO, ESMO, ISPOR. In addition to the formal literature search and hand searches, the NICE website was searched to identify relevant information from previous submissions not otherwise captured.

Appendix 21 provides details relative the eligibility criteria for the HRQoL literature search along with details of the search strategy for the health related quality of life and utilities.

A total of 860 papers were identified in the HRQoL and utilities search (Figure 30).

Figure 30: PRISMA Diagram: HRQoL and Utility studies



Key: *HRQoL, Health-related quality of life.*

As no study assessing patients naïve to treatment with ipilimumab before entering the study was identified, the search was widened to patients with advanced melanoma and 11 studies were identified meeting the inclusion criteria. The list of studies identified is presented in Table 74.

5.4.4 Provide details of the studies in which HRQoL was measured

Table 74: Characteristics of the HRQoL and utility studies identified

Authors	Date	Population	Setting	Method of derivation	Utilities included	SD/SE/range or CI's
Askew et al.[107]	2011	Melanoma Stage III: N=100 Stage IV: N=71	US	Mapping the FACT-M to the EQ-5D	Stage III: 0.85 Stage IV: 0.86	SD: Stage III: 0.13 Stage IV: 0.11
Barzey et al.[116]	2013	Patients with pre-treated advanced melanoma N=140	US	Not stated	Complete / partial response: 0.88 Stable disease: 0.80 Progressive disease: 0.52 Death: 0	Lower and Upper Bounds: Complete / partial response: 0.70-1.00 Stable disease: 0.64-0.96 Progressive disease: 0.42-0.62
Batty et al.[114]	2011	Advanced melanoma	UK	Standard Gamble, SF-36 mapped to the SF-6D and the EORTC QLQ-C30 mapped to the EORTC-8D	EORTC QLQ-C30: Pre-progression: 0.80 Post-progression: 0.76 SF-36: Pre-progression: 0.64 Post-progression: 0.62	
Batty et al.[108]	2012	Advanced melanoma	UK	EORTC QLQ-C30 mapped to the EORTC-8D	Pre-progression: 0.80 Post-progression: 0.76	
Beusterien et al.[106]	2009	Advanced melanoma UK: n=63 Australia: n=77	UK and Australia	Standard gamble technique was used to elicit 13 health states from 140 respondents	UK: Partial response: 0.85 Stable disease: 0.77 Progressive disease 0.59 Best supportive care: 0.59	SE: UK: Partial response: 0.02 Stable disease: 0.02 Progressive disease:

Authors	Date	Population	Setting	Method of derivation	Utilities included	SD/SE/range or CI's
					All (UK and Australia): Partial Disease: 0.88 Stable disease: 0.80 Progressive disease 0.52 Best supportive care (BSC): 0.52	0.02 Best supportive care: 0.02 All (UK and Australia): Partial Disease: 0.01 Stable disease: 0.01 Progressive disease 0.02 Best supportive care (BSC): 0.02
Dixon et al.[109]	2006	Malignant melanoma: 3 months: n=80 6 months: n=74 12 months: n=66 24 months: n=31 36 months: n=25 48 months: n=12 60 months: n=10	UK	EQ-5D was used to elicit utilities	3 months: 0.7734 6 months: 0.8204 12 months: 0.8170 24 months: 0.8258 36 months: 0.8270 48 months: 0.8718 60 months: 0.8493	SD: 3 months: 0.23744 6 months: 0.16180 12 months: 0.21418 24 months: 0.20847 36 months: 0.13076 48 months: 0.13564 60 months: 0.20560
Hatswell et al.[110]	2014	advanced or metastatic melanoma	Patients enrolled at 125 centers in 13 countries in North America, South America, Europe, and Africa	Utilities were generated from the ipilimumab MDX010-20 trial using the condition-specific EORTC QLQ-C30 (via the EORTC-8D) and generic SF-36v2 (via the SF-6D) preference-based measures	**EORTC-8D** **Progression:** Pre-progression: 0.803 Post-progression: 0.755 **Time to death:** 180 or more days to death: 0.831 120 - 179 days to death: 0.771 90 - 119 days to death: 0.763 60 - 89 days to death: 0.720 30 - 59 days to death: 0.679	

Authors	Date	Population	Setting	Method of derivation	Utilities included	SD/SE/range or CI's
					Under 30 days to death: 0.653 **SF-6D** **Progression:** Pre-progression: 0.642 Post-progression: 0.612 **Time to death:** 180 or more days to death: 0.667 120 - 179 days to death: 0.616 90 - 119 days to death: 0.613 60 - 89 days to death: 0.585 30 - 59 days to death: 0.557 Under 30 days to death:0.544	
Hogg et al.[117]	2010	Advanced melanoma N=87	Canada	Standard gamble was used to elicit utilities in advanced melanoma from 87 respondents	Partial response: 0.84 Stable disease: 0.79 Progressive disease: 0.55 BSC: 0.54	SE: Partial response: 0.02 Stable disease: 0.02 Progressive disease: 0.02 BSC: 0.02
King et al.[118]	2011	Melanoma Stage III: n=8 Stage IV: n=11		Time trade-off (TTO) technique and a computer based utility generator was used to elicit utilities of different stages of melanoma patients from 163 respondents	New Diagnoses: Stage III mean: 0.534 Stage III median: 0.595 Stage IV mean: 0.693 Stage IV median:0.731 Established Diagnoses: Stage III mean: 0.908 Stage III median: 0.940 Stage IV mean: 0.527	New Diagnoses: Stage III mean SD: 0.291 Stage III median IQR: 0.275-0.720 Stage IV mean SD: 0.329 Stage IV median IQR: 0.280-1.00 Established

Authors	Date	Population	Setting	Method of derivation	Utilities included	SD/SE/range or CI's
					Stage IV median:0.500	Diagnoses: Stage III mean SD: 0.123 Stage III median IQR: 0.897-1.00 Stage IV mean SD: 0.339 Stage IV median IQR: 0.246-0.864
Lee et al.[119]	2012	Previously -treated metastatic melanoma N=313	UK	EORTC QLQ-C30 mapped to the EORTC-8D	Progression Free Disease: 0.80 Progressive Disease: 0.76	
Tromme et al.[120]	2014	Melanoma patients Stage IV-T n=41 Stage IV-R n=14	Belgium	EQ-5D-5L, VAS and FACT-M EQ-5D-5L states into a utility	Utilities* Stage IV-T From start of treatment 0.583 Stage IV-R From start of remission 0.796	Utilities* Stage IV-T from start of treatment: SD: 0.192 CI: (0.524;0.642) Stage IV-R from start of remission: SD: 0.167 CI: (0.708;0.883)

5.4.5 Key differences between the values derived from the literature search and those reported in or mapped from the clinical trials

Table 74 provides a summary of the studies identified following a systematic literature search on health related quality of life which identified 11 studies in advanced melanoma.

Overall, the utilities derived from the KEYNOTE-006 trial are comparable to those found in other trial based studies. Ipilimumab utilities reported in the previously untreated NICE STA submission[3] derived using the EORTC-8D, are slightly higher than the ones reported in the KEYNOTE-006 trial for time to death (Table 75), especially when patients are closer to death (i.e. 30 days from death). This could be partly explained by

the fact that in the KEYNOTE-006 trial patients were slightly sicker than in the trial supporting the ipilimumab previously untreated NICE STA submission (CA184-024)[3] and the fact that OS data was immature at time of the IA1 when the EQ-5D analysis was done. In addition, the questionnaires were administered via electronic devices which may have also impacted the results.

Table 75: Comparison of utilities reported used in both ipilimumab previously untreated and KEYNOTE-006 economic models

Time to death (days)	MK3475 10 mg, Q3w					Ipilimumab					Pooled					First-line ipilimumab NICE submission (TA319)[3]	
	n[†]	n[‡]	Mean	SE	95% CI	n[†]	n[‡]	Mean	SE	95% CI	n[†]	n[‡]	Mean	SE	95% CI	Utility value	(95% CI)
≥360[*]	110	219	0.83	0.01	(0.80, 0.85)	76	168	0.80	0.02	(0.77, 0.84)	186	387	0.82	0.01	(0.79, 0.84)	0.885	(0.853 – 0.917)
[270, 360)	18	34	0.71	0.05	(0.60, 0.82)	19	30	0.71	0.06	(0.59, 0.82)	37	64	0.71	0.04	(0.63, 0.79)	0.880	(0.847 – 0.912)
[180, 270)	35	67	0.64	0.04	(0.55, 0.73)	28	45	0.69	0.04	(0.60, 0.77)	63	112	0.66	0.03	(0.60, 0.72)	0.854	(0.823 – 0.885)
[90, 180)	38	67	0.66	0.04	(0.58, 0.73)	38	62	0.65	0.04	(0.57, 0.74)	76	129	0.66	0.03	(0.60, 0.71)	0.810	(0.780 – 0.840)
[30, 90)	20	24	0.56	0.07	(0.42, 0.70)	31	49	0.57	0.05	(0.47, 0.68)	51	73	0.57	0.04	(0.49, 0.65)	0.739	(0.710 – 0.768)
<30	10	12	0.47	0.13	(0.18, 0.76)	8	8	0.12	0.15	(-.23, 0.46)	18	20	0.33	0.10	(0.11, 0.55)	0.631	(0.600 – 0.668)

[†] n=Number of patient with non-missing EQ-5D index score
[‡] n=Number of records with non-missing EQ-5D index score
EQ-5D index scores during baseline are not included
[*] This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days.

The progression-based utilities derived from the KEYNOTE-006 trial[3] are similar, although slightly higher, to those found in the KEYNOTE-002 trial.[22] This is line with expected results as quality of life would be expected to be higher in patients in first-line compared to patients previously treated.

Other values have been published that are in line with the values previously mentioned. All these available values from published sources seem to report higher utilities than those estimated in KEYNOTE-006, which may be due to the poorer prognosis of the patients included in this

trial. As described in the ipilimumab previously untreated NICE STA (TA319),[3] Askew et al[107] found an average utility of 0.86 for stage IV patients and Dixon et al[109] found an average utility of 0.77 at 3 months and 0.87 at 48 months of follow-up.

5.4.6 Describe how adverse reactions affect HRQoL

Immunotherapy checkpoint inhibitors, such as ipilimumab and pembrolizumab, are associated with a broad range of AEs, particularly immune-related, that can affect the HRQoL of patients, and that can be serious or fatal.

Section 4.12.2 reports the AEOSIs associated with use of pembrolizumab in the 10mg/kg treatment arms versus ipilimumab in KEYNOTE-006.

Table 76: EQ-5D Health Utility Scores in progression-free state: with and without Grade 3-5 AEs (progression by IRO assessment)

	MK3475 10 mg, Q3w					Ipilimumab					Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
During Grade3-5 AEs	34	73	0.57	0.04	(0.50, 0.65)	42	93	0.57	0.04	(0.49, 0.64)	76	166	0.57	0.03	(0.52, 0.62)
Without Grade3-5 AEs	216	610	0.83	0.01	(0.82, 0.85)	179	401	0.81	0.01	(0.79, 0.83)	395	1011	0.82	0.01	(0.81, 0.83)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline is not included

A statistically significant difference in utility has been found for patients experiencing grade 3 to 5 AEs across all treatment arms compared to patients who did not experience these events. Table 77 reports the EQ-5D utilities from KEYNOTE-006 following assessment by IRO. Analysis of utilities of grade 3-5 AEs for patients in progression-free state is presented in Table 76, when patients experience a grade 3-5 AE, and when they do not.

It has been assumed for the purposes of the modelling that any impact of AEs on HRQoL was already captured within the EQ-5D scores obtained from KEYNOTE-006 and no further decrement has been applied. This is a conservative assumption given that the AE profile of pembrolizumab is favourable compared with those of ipilimumab, vemurafenib and dabrafenib.

5.4.7 Definition of the health states in terms of HRQoL in the cost-effectiveness analysis.

HRQoL utilities based upon time to death decrease over time as patients progress closer to death. However, progression related utilities do not show a large difference between pre and post-progression utilities, indicating that progression status alone is unlikely to be sufficiently reflective of changes in quality of life.

5.4.8 Clarification on whether HRQoL is assumed to be constant over time in the cost-effectiveness analysis

A constant value for HRQoL is applied in each cycle according to time to death and a utility decrement of 0.0039 per year is applied from the age of 60 until 75 to reflect the natural decrease in utility associated with increasing age.

5.4.9 Description of whether the baseline HRQoL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states

Not applicable.

5.4.10 Description of how and why health state utility values used in the cost-effectiveness analysis have been adjusted, including the methodologies used

The health state utility values have not been amended; however, as explained above, a yearly utility decrement applies as patients get older (above 60 until 75).

5.4.11 Identification of any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis

No health effects were excluded from the cost effectiveness analysis. HRQoL in the base case scenario is based upon time to death rather than progression as clinical opinion has

suggested that there is a decline in HRQoL in the final months of life of advanced melanoma patients and this approach was previously accepted in the ipilimumab 1L submission (TA319).[3]

5.4.12 Summary of utility values chosen for the cost-effectiveness analysis, referencing values obtained in sections 5.4.1–5.4.6.

The utility values chosen for the cost-effectiveness model are presented in Table 77.

Table 77: Summary of utility values for cost-effectiveness analysis

	Utilities**		Reference in submission (section and page number)	Justification
	Mean	95% CI		
Base case - Time to Death (days) (KEYNOTE-006)				
≥360*	0.82	(0.79, 0.84)	Section 5.4.5 Table 75 Page 194	Reported EQ-5D utilities in line with NICE reference case.[112] Use of time to death utilities previously accepted in NICE TA319.[3]
[270, 360)	0.71	(0.63, 0.79)		
[180, 270)	0.66	(0.60, 0.72)		
[90, 180)	0.66	(0.60, 0.71)		
[30, 90)	0.57	(0.49, 0.65)		
<30	0.33	(0.11, 0.55)		
Sensitivity analysis - Time to Death (days) (TA319)[3]				
≥360*	0.82	(0.79, 0.84)	Section 5.4.5 Table 75 Page 194	Alternative utility values from published data
[270, 360)	0.71	(0.63, 0.79)		
[180, 270)	0.66	(0.60, 0.72)		
[90, 180)	0.66	(0.60, 0.71)		
[30, 90)	0.57	(0.49, 0.65)		
<30	0.33	(0.11, 0.55)		
Sensitivity analysis - progression based utilities (KEYNOTE-006)				
Progression-Free	0.8	(0.78, 0.81)	Section 5.4.1 Table 75 Page 187	Alternative utility values from KEYNOTE-006
Progressed	0.7	(0.67, 0.73)		
Sensitivity analysis - progression based utilities (Batty 2011)[114]				
Progression-Free	0.8	Not available	Not applicable	Alternative utility values from published data
Progressed	0.76	Not available		

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included
** This group also includes patients whose death dates were censored and report EQ5D ≥ 180 days.*
*** Utilities from KEYNOTE-006 are pooled utilities*

5.4.13 Details if clinical experts assessed the applicability of the health state utility values available or approximated any of values

As previously mentioned, the utility values used in the economic model are in line, although slightly lower, with those from the submission for ipilimumab as first-line treatment (TA319)[3]

and from utilities reported in the literature. As such, it was not deemed necessary to consult clinicians to assess the applicability of the heath state utility values.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Parameters used in the cost effectiveness analysis

A summary of the variables used in the cost estimation is presented in Appendix 22.

5.5.2 Resource identification, measurement and valuation studies

The type of costs included in the model aimed to reflect the clinical management of patients with unresectable or metastatic melanoma and included: treatment costs (including drug and administration), monitoring and follow-up of patients, management of complications and AEs, and terminal care.

A systematic literature review was conducted with the aim of identifying resource requirements and costs associated with the treatment of advanced melanoma patients (covering those patients who have unresectable or metastatic melanoma). The population criteria considered in the systematic review were broader than unresectable or metastatic melanoma to ensure the review captured sufficient relevant information to be of use to populate the economic model. From 2,742 references initially identified, seven studies reported costs and/or resource use data for advanced melanoma patients.[53;109;119;121-124] However, none of these studies specifically reported on patients naïve to treatment with ipilimumab. From an updated search conducted in March 2015 no additional relevant cost studies were identified for inclusion, although one additional study was identified from hand-searches afterwards.[125] The searches conducted for resource use data and the selection criteria followed for the identification and inclusion of relevant studies are provided in Appendix 23 and Appendix 24, respectively. A summary presenting the details of the included studies is available in Appendix 25.

All included studies were in the UK setting. The MELODY study represents the largest single study of resource utilisation in melanoma (n=220).[121;122] It reported resource utilisation for a UK-specific cohort and has been widely cited given that it is the only study that has formally reported resource utilisation in terms of inpatient, outpatient and hospice care requirements. This study, however, predates the availability of both ipilimumab and BRAF inhibitors. Additionally, the average annual GP consultation rate per new case of melanoma was reported in a different UK study.[53]

5.5.3 Use of NHS reference costs or payment-by-results (PbR) tariffs

There are no NHS reference costs or payment-by-results (PbR) tariffs specific for costing pembrolizumab. Details about the cost estimation of treatment with pembrolizumab in terms of acquisition and administration are reported below. It was agreed with NHS England (personal communication) that the NHS Reference Cost code SB12Z could be used to estimate the administration cost of pembrolizumab since this corresponds to the administration of a simple therapy (i.e. involving the administration of only one agent without IV anti-emetics) and the infusion only lasts half an hour.

5.5.4 Input from clinical experts

A recent submission for ipilimumab as a first-line therapy (TA319) included estimates of resource use based on the MELODY study.[3] These estimates were accepted by the Committee as reasonable for the population under consideration. As such, it was not deemed necessary to consult clinicians to determine appropriate resource use and the approaches taken in this submission are broadly in line with those taken in TA319.

5.5.5 Intervention and comparators' costs and resource use

The following costs were incorporated in the economic model to reflect the costs related to the intervention and comparator: acquisition and administration of the study medications (the latter including the corresponding monitoring costs per administration) and the management of AEs (as described below). Details about the costs related to the management of AEs are provided in section 5.5.7.

Drug costs

Pembrolizumab

As per licence, the model uses a 2mg/kg dose of pembrolizumab, administered as a 30-minute IV infusion every 3 weeks (Q3W) (see Appendix 1). The list price of a 50mg vial is £1,315 (pending final confirmation with Department of Health). In order to estimate the average number of vials required per patient treated with pembrolizumab, a calculation using the patient weight distribution from the KEYNOTE-006 clinical trial was performed. The proportions of males and females per weight interval were used for the calculation of the mean number of vials per patient, assuming no vial sharing (see

Table 78). The average number of vials of pembrolizumab required per patient was 3.7. This calculation used only the European patients from the KEYNOTE-006 trial to be most representative of the UK population.

Table 78: Weight distribution and average number of vials (European patients)[126]

Pembrolizumab	% among males	% among females	Upper Target Dose	No. of vials
0-50 kg	0.00%	4.95%	100	2
51-75 kg	26.99%	59.34%	150	3
76-100 kg	60.18%	33.52%	200	4
101-125 kg	10.62%	2.20%	250	5
126-150 kg	1.77%	0.00%	300	6
151-175 kg	0.44%	0.00%	350	7
175-200 kg	0.00%	0.00%	400	8
Mean Number of Vials per Patient (assuming no vial sharing)				3.7

Ipilimumab

As per ipilimumab SmPC,[127] the model assumed that a 3mg/kg dose of ipilimumab is to be administered as a 90-minute IV infusion every 3 weeks (Q3W) for 4 doses. The list prices of a 50mg/10ml vial and of a 200mg/40ml vial are respectively £3,750 and £15,000. For simplicity the model only considered the 50mg/10ml vial, since the cost per milligram is the same independent of the vial size. This is consistent with the approach taken to estimate the average number of vials of ipilimumab required in the ipilimumab first-line submission (TA319).[3] For the purpose of representativeness, to estimate the average number of vials required per patient treated with ipilimumab the patient weight distribution from the KEYNOTE-006 European patients was taken into account. The proportions of males and females per weight interval were accounted for in the calculation of the mean number of vials per patient, assuming no vial sharing (see

Table 78). The average number of vials of ipilimumab required per patient in the KEYNOTE-006 trial was 5.7 (see Table 79).

Table 79: Ipilimumab dosing schedule

Ipilimumab	No. of vials
0-50 kg	3
51-75 kg	5
76-100 kg	6
101-125 kg	7
126-150 kg	8
151-175 kg	10
175-200 kg	11
Mean Number of Vials per Patient (assuming no vial sharing)	5.7

To estimate the drug cost for pembrolizumab and ipilimumab we considered evidence from KEYNOTE-006 relative to the proportion of patients who had not progressed and received the scheduled dose (see Table 80).

Given the relatively low numbers of patients with advanced melanoma per centre in the UK, implementing vial sharing in practice may be challenging. Therefore, vial sharing was not accepted by NICE in past submissions. Our base case has therefore assumed no vial sharing. Sensitivity analyses were conducted to assess the impact around the feasibility of implementing vial sharing to reflect the situation of centres where a higher number of advanced melanoma patients are treated and therefore the implementation of vial sharing may be feasible.

Vemurafenib

As per vemurafenib SmPC,[128] the recommended dose is 960mg (4 tablets of 240mg) twice daily (equivalent to a total daily dose of 1,920mg). Treatment with vemurafenib should continue until disease progression or the development of unacceptable toxicity. Vemurafenib is provided in a pack of 56 tablets which represents the weekly amount required (i.e. 8 tablets of 240mg is required daily). The cost of a pack of 56 tablets is £1,750. For the purpose of the economic model (and given lack of available evidence to assume otherwise), patients were assumed to receive 100% of the expected dose (see Table 80).

Dabrafenib

As per dabrafenib SmPC,[129] the recommended dose is 150mg (2 capsules of 75mg) twice daily (corresponding to a total daily dose of 300mg). Treatment with dabrafenib should continue until the patient no longer derives benefit or the development of unacceptable toxicity. The cost of a 50mg 28-capsules pack and a 75-mg capsules pack are respectively £933.33 and £1,400, the latter representing the weekly cost associated with the use of dabrafenib. For the purpose of the economic model, it is assumed that patients will receive 100% of the expected dose (see Table 80).

The proportion of patients receiving the expected dose is reported in Table 80.

Table 80: Proportion of patients receiving expected dose

	Number of patients in each cycle of ipilimumab (PFS)	Number Treated	Proportion receiving dose expected for PFS
Pembrolizumab	-	277	87.7%
Ipilimumab - dose 1	256.00	256.00	100.0%
Ipilimumab - dose 2	247.00	237.00	96.0%
Ipilimumab - dose 3	224.00	194.00	86.6%
Ipilimumab - dose 4	192.00	156.00	81.3%
Vemurafenib	-	-	100.0%
Dabrafenib	-	-	100.0%
Key: *PFS, progression-free survival*			

Number of administrations required, unit costs and total drug costs per treatment per cycle

As per the licence, patients are expected to be treated until disease progression is confirmed. Therefore, PFS has been used as a proxy for the time on treatment with pembrolizumab, with an adjustment based on actual proportion of patients receiving the expected dose within KEYNOTE-006. For this, dose interruption and early stopping due to toxicity were analysed from the KEYNOTE-006 data and incorporated into the model per administered cycle of pembrolizumab and ipilimumab. These analyses showed that, on average, 87.7% of patients on pembrolizumab received their expected doses.

The unit costs per pack or vial of treatment administered (for pembrolizumab, ipilimumab, vemurafenib and dabrafenib) are presented in Table 81. A patient access scheme (PAS) is in place for ipilimumab, vemurafenib and dabrafenib. We have also proposed a PAS for pembrolizumab. The level of discount presented in the comparators schemes is unknown therefore the list prices are presented in Table 81.

Table 81: Treatment cost per pack/vial

Treatment	Pack size/vial volume	Cost per pack/vial	Source
Pembrolizumab	50mg vial	£1,315	Pending confirmation with Department of Health
Ipilimumab	5mg/ml vial concentration		
	10ml (50mg) vial	£3,750	MIMS 2015: 5mg/ml, 10-ml vial [130]
	40ml (200mg) vial	£15,000	MIMS 2015: 5mg/ml, 40-ml vial [130]
Vemurafenib	240mg 56-tab pack	£1,750	MIMS 2015: 240mg 56-tab pack [130]
Dabrafenib	50 mg, 28-cap pack	£933.33	MIMS 2015: 50 mg, 28-cap pack [130]
	75 mg, 28-cap pack	£1,400	MIMS 2015: 75 mg, 28-cap pack [130]

Administration costs

Administration costs have been sourced from NHS reference costs[131] and are shown in Table 82. The base case costs used for administration are presented in Table 83.

Pembrolizumab

Given the time required for the administration of pembrolizumab is 30 minutes (see Appendix 1), the code for 'simple parenteral chemotherapy – outpatient' SB12Z was used to reflect administration costs.[132] This was considered an appropriate approach as it was agreed with NHS England for EAMS patients. The administration costs are presented in Table 82 and Table 83.

Ipilimumab

As per the SmPC of ipilimumab,[127] the time required per administration is 90 minutes every 3 weeks. Consequently, the unit cost considered for the administration of ipilimumab (for initial and subsequent administrations) relates to code SB13ZZ (i.e. "deliver more complex parenteral chemotherapy at first attendance – day case and regular day/night"). The SmPC of ipilimumab also indicates that liver and thyroid function tests should be performed prior to each dose being administered. Therefore, a single complete metabolic panel cost has also been accounted for at each administration of ipilimumab (see Table 82 and Table 83).

Vemurafenib

In line with the approach taken in the ipilimumab first-line NICE submission,[3] since vemurafenib is an oral agent, the administration cost "Deliver exclusively Oral Chemotherapy – outpatient" was applied to the first cycle only as an outpatient appointment. Subsequent doses were assumed to be taken orally at home. As per vemurafenib submission[16] a pharmacy costs, to dispense and check a prescription every 28 days, was taken into account in the calculation of the administration costs. An average of 12 minutes of pharmacist time for dispensing vemurafenib was accounted for and applied to the hourly cost of a pharmacist

time. The cost of a pharmacist time was derived from the PSSRU 2014.[133] The administration costs are presented in Table 82 and Table 83.

Dabrafenib

A similar approach to the one taken for vemurafenib was applied to dabrafenib as these two oral agents are administered in a similar manner (i.e. only one administration cost applied to the first cycle). The administration costs are presented in Table 82 and Table 83.

Table 82: NHS reference costs and PSSRU costs – administration of treatments[131]

Type	Source	Unit Price
Deliver simple parenteral chemotherapy at first – Daycase	NHS Reference Costs 13/14 SB12Z-Daycase	£245.17
Deliver more complex Parenteral Chemotherapy at first attendance – Daycase	NHS Reference Costs 13/14 SB13Z – Daycase	£316.95
Deliver exclusively oral chemotherapy – outpatient	NHS Reference Costs 13/14 SB11Z-Chemotherapy outpatient	£136.48
Single complete metabolic panel	NHS Reference Costs 2013/14 DAPS04	£1
Cost of one hour of pharmacist time	PSSRU (2014); Hospital pharmacist - cost for direct clinical patient time including qualifications	£96

Key: *NHS, National Health Service; PSSRU, Personal Social Services Research Unit.*

Table 83: Administration Costs used in the model[131]

Treatment	Type of Administration Required	Daycase or Outpatient	Cost
Pembrolizumab	Simple Chemotherapy	Daycase	£245.17
Ipilimumab	Complex chemotherapy	Day case	£317
Vemurafenib	Oral chemotherapy	Outpatient	£136.48
Dabrafenib	Oral chemotherapy	Outpatient	£136.48

5.5.6 Health-state unit costs and resource use

Due to the relatively recent approval of ipilimumab and BRAF inhibitors, the treatment algorithm for unresectable or metastatic melanoma patients in the UK is rather dynamic at present. Moreover, there are a large number of new agents that are currently under investigation for advanced melanoma in the UK. As a consequence, many patients are treated in clinical trials rather than in routine clinical practice.

In the manufacturer's submissions for ipilimumab (TA319)[3] a micro-costing approach was implemented and the list of patient resource use was presented. Resource use data was sourced from the MELODY study.[122] This was still considered to be the most appropriate source for resource data for pembrolizumab as there were no other alternative sources identified from the economic literature review. Therefore, the healthcare resource utilisation data used to populate health state costs was mainly obtained from the MELODY study.[122] This study had been commissioned and used as part of previous manufacturer's NICE submissions[2;3] and it was the source most likely to reflect UK clinical practice. However, its limitations should be recognised; for example, the study predated the new melanoma treatments currently approved and recommended; additionally, patients were recruited 8-10 years ago, and as such the clinical landscape may differ considerably to UK practice today, particularly given the availability of ipilimumab and available treatments for BRAF-mutation positive melanoma. Dacarbazine, the most widely used treatment among patients in the MELODY study, is now used only when no active treatment is available.

The resource use from the MELODY study[122] and from the manufacturer's submission for ipilimumab in first-line[3] and the corresponding unit costs used in this submission are presented in Appendix 26. Depending on the health state patients were in, the use of resources related to outpatient and inpatient care, home care, radiologic exams and terminal care, were applied in the following way:

- In the pre-progression health state there were two types of costs applicable:
    - For patients at the point of treatment initiation, a 'first line treatment initiation' cost was applied during the first treatment cycle.
    - Patients remaining without progression after treatment initiation were allocated the following:
        - A 'first or second line treatment' cost while receiving treatment
        - A cost when they were 'not receiving treatment'
- For patients experiencing progression, the cost of BSC was applied.
- Patients in the period just before dying were assumed to require palliative/terminal care, which was defined as 'Terminal Care applied On Death' and related to hospital care in the 90 days before dying, based on Georghiou & Bardsley (2014).[134] The costs of terminal care included services such as emergency inpatient admissions, non-emergency inpatient admissions, outpatient attendances and accident and emergency costs.[134] In the base case this cost was applied as a one off cost at the point of death, however scenario analyses are considered applying this as a weekly cost over the final 90 days before death and using an alternative source.[134;135]

Costs for BRAF mutation testing have not been included in the model as this takes place prior to this line of therapy.

To reflect the scope of the decision problem, no further lines of treatment were modelled. Instead, we assumed that, once progressing, all patients would receive BSC (see section 5.2.2). Therefore, for patients who progressed after the initial therapy, the cost of BSC was considered. Data used to estimate costing of BSC is presented in Appendix 27.

5.5.7 Adverse reaction unit costs and resource use

The type of AEs included were those considered to have a significant impact in terms of either resource utilisation or HRQoL. Mainly Grade 3 or 4 AEs experienced by more than 3% of patients or that were noted to be expensive to manage (including: fatigue, rash, nausea/vomiting, arthralgia, myalgia/pain, skin reaction, respiratory distress/pulmonary oedema, anaemia, neutropenia, palmar-plantar erythrodysesthesia, pyrexia, squamous cell carcinoma, keratocanthoma) were included. Some additional AEs of lower grade were incorporated because they were expected to have a high cost or HRQoL impact despite their lower grade (e.g. diarrhoea grade 2 or above, colitis any grade and endocrine disorders all grades). The incidence of AEs for patients treated with pembrolizumab and ipilimumab used in the model was obtained from KEYNOTE-006 (see section 4.12), while the incidence of AEs for patients treated with vemurafenib and dabrafenib were obtained from their trial publications.[8;30] The unit costs were mainly derived from TA 319,[3] which referred to the MELODY study as the main data source (see Table 84) and from TA269.[16] Hypotension, dyspnoea, photosensitivity, leukopenia, thrombocytopenia, hyponatremia and decreased platelet count were assumed to incur a null cost, as for previous submissions.[3;136] The 'other cost' category is associated to costs that were not clearly identified as being inpatient or outpatient costs in previous submissions.[16;17]

Table 84: Adverse events costs

Adverse events	Items	Value	Source
Fatigue	Inpatient Cost & %	£596.38, 10%	Ipilimumab 1L submission[3] inflated to 2014 costs
	Outpatient Cost & %	£156.84, 90%	
	Average Cost per Patient	£200.79	
Diarrhoea	Inpatient Cost & %	£838.46, 50%	Ipilimumab 1L submission[3] inflated to 2014 costs
	Outpatient Cost & %	144.05, 50%	
	Average Cost per Patient	£491.26	
Rash	Other cost & %	£137.31, 100%	Vemurafenib submission[16]
Nausea and vomiting	Inpatient Cost & %	£838.46, 10%	Assumed the same as diarrhoea
	Outpatient Cost & %	£144.05, 90%	

Adverse events	Items	Value	Source
	Average Cost per Patient	£213.49	
Arthralgia	Outpatient Cost & %	£171.86, 100%	HRG service code: 191, Pain management, multi-professional non-admitted face-to-face (WF02A, consultant led outpatient attendance); NHS reference costs 2013/14[131]
Colitis	Inpatient Cost & %	£1,011.21, 100%	Ipilimumab 1L submission[3] inflated to 2014 costs
Myalgia/pain	Outpatient Cost & %	£171.86, 100%	HRG service code: 191, Pain management, multi-professional non-admitted face-to-face (WF02A, consultant led outpatient attendance); NHS reference costs 2013/14[131] (as per TA 319[3])
Skin reaction	Inpatient Cost & %	£1,2332.38, 5.20%	Ipilimumab 1L submission[3] inflated to 2014 costs
	Outpatient Cost & %	£199.09, 94.80%	
	Average cost per patient	£252.82	
Respiratory distress/pulmonary oedema	Inpatient Cost & %	£1,767.57, 100%	DZ20C, Pulmonary Oedema with CC score 0-3, NHS Trusts Non-Elective Inpatient (Long Stay) HRG Data; NHS reference costs 2013/14 as per TA319[3]
Anaemia	Inpatient Cost & %	£596.38, 50%	Assume the same as fatigue
	Outpatient Cost & %	£156.84, 50%	
	Average Cost per Patient	£376.61	
Endocrine Disorders	Inpatient Cost & %	£579.88, 33.2%	Ipilimumab 1L submission[3] inflated to 2014 costs
	Outpatient Cost & %	£441.09, 66.8%	
	Average Cost per Patient	£487.17	
Neutropenia	Inpatient Costs & %	£1,619.70 , 30%	Ipilimumab 1L submission[3] inflated to 2014 costs
	Outpatient Costs & %	£205.01, 70%	
	Average Cost per Patient	£629.42	
Palmar-plantar erythrodysesthesia	Other cost & %	£137.31, 100%	Assumed to have the same cost as Grade 3 or higher rash as per TA321[17]
Pyrexia	Inpatient Costs & %	£3,487.13, 100%	NHS reference costs 2013/14, Pyrexia of unknown origin with length of stay 5 days or more WA05Z (weighted average of non-elective short stay: £474.99 (16) and non-elective long-stay: £3515.08 (1724)[131]
Squamous cell carcinoma	Other cost & %	£164.36, 100%	NHS Reference Costs 2013/14 – JC41Z: Outpatient major skin procedure as per TA269[16]

Adverse events	Items	Value	Source
Keratocanthoma	Other cost & %	£164.36, 100%	NHS Reference Costs 2013/14 – JC41Z: Outpatient major skin procedure as per TA269[16]
Thrombocytopenia	Outpatient Cost and %	£316.00, 100%	NHS reference costs 2013/14[131] Thrombocytopenia Daycase SA12K
	Average Cost per Patient	£316.00	
Leukopenia	Cost assumed £0		Cost assumed £0
Hypotension	Cost assumed £0		Cost assumed £0
Dyspnoea	Cost assumed £0		Cost assumed £0
Photosensitivity	Cost assumed £0		Cost assumed £0
Hyponatremia	Cost assumed £0		Cost assumed £0
Platelet count decreased	Cost assumed £0		Cost assumed £0
Key: *1L, first-line; NHS, National Health Service*			

5.5.8 Miscellaneous unit costs and resource use

There are no additional costs included in the model apart from those outlined in the previous sections.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Tabulated variables included in the cost-effectiveness analysis

Please find in Appendix 22 a summary of the variables applied in the economic model.

5.6.2 For the base-case de novo analysis the company should ensure that the cost-effectiveness analysis reflects the NICE reference case as closely as possible

The base-case cost-effectiveness analysis reflects the NICE reference case.

5.6.3 List of all assumptions used in the de novo economic model with justifications for each assumption

Table 85 summarised the assumptions used in the economic model.

Table 85: List of assumptions used in the economic model

Area	Assumption	Justification
Comparator	The relevant comparators are: ipilimumab, vemurafenib ($BRAF^{v600}$ positive mutation) and dabrafenib ($BRAF^{v600}$ positive mutation).	These are treatments which are approved by NICE for use in the NHS in England. Dacarbazine is administered to alleviate symptoms in the palliative setting but it does not result in an improvement in OS.[12;13] Therefore, dacarbazine is not considered to be current clinical practice in the first line setting.

Area	Assumption	Justification
Treatment pathway	Once patients progress they receive palliative care	A three state model was preferred over a treatment sequencing model by the ERG and Committee during the ipilimumab first-line submission (see Section 5.5.2)
Time horizon	30 years	The average age of patients in the model is 60. Lifetime horizon is in line with NICE reference case and as per TA268,[2] TA269[16] and TA321,[17] 30 years is long enough to reflect the difference in costs and outcomes between the technologies being assessed in this submission.
Population	Endpoints obtained from KEYNOTE-006 are applicable to all patients independent of their BRAF status	The KEYNOTE-006 trial did not suggest that there was a difference in efficacy for pembrolizumab compared with ipilimumab based on $BRAF^{V600}$ mutation status.
Efficacy Comparator	Pembrolizumab expected to show a similar improvement in survival vs. ipilimumab over time compared to that observed in the KEYNOTE-006 trial	The results of the KEYNOTE-006 trial demonstrated that pembrolizumab resulted in significant improvement in OS (see Section 4.7).[18] Since pembrolizumab is an immunotherapy like ipilimumab, it is expected that it would have a similar survival profile in the long-term.[9]
HRQoL	The quality of life of patients is more appropriately captured by time to death rather based on progression-based utilities	Clinical opinion suggests there is a decline on HRQoL in the final months of life of advanced melanoma patients which may not appropriately be captured solely through the use of progression-based health state. As per previous NICE submission (TA319)[3] the approach based on time to death utilities was used. Progression-based utilities were further assessed in sensitivity analyses.
Safety	The incidence of AEs from KEYNOTE-006 trial was assumed to reflect that observed in clinical practice	Assumption based on the results of the KEYNOTE-006 trial(i.e. grade 3-5 AEs (incidence≥1% in one or more treatment groups (APaT population))
	The cost of diarrhoea grade 2+ in addition to costs associated to grade 3-5 AEs which had an incidence greater than 3% were considered since they incurred in relevant resource utilisation.	Consistent with approach taken in ipilimumab previously treated submission (TA268).[2]
Costs	Vial sharing is not allowed.	Given the relatively low numbers of patients with advanced melanoma per centre in the UK, implementing vial sharing in practice may be challenging. Therefore, vial sharing was not accepted by NICE in past submissions. Our base case has therefore assumed no vial sharing.
	BSC is applied as an average weekly cost for up to 7 cycles.	This is a simplifying assumption which is in line with the ipilimumab first-line submission[3] and has been made in order to apply a cost of BSC following progression without over-complicating the model.
Resource use	Based on MELODY study.	Due to the relatively recent approval of ipilimumab and BRAF inhibitors, the treatment algorithm for unresectable or metastatic melanoma patients in the UK is uncertain at present. Resource use data sourced from the MELODY study has therefore been used, consistent with TA319.[3] This was still considered to be the most appropriate source for resource data for pembrolizumab as there were no other alternative sources identified from the economic literature review.

5.7 Base-case results

5.7.1 Base-case cost effectiveness analysis results

The results of the economic model for patients with $BRAF^{V600}$ wild type mutations and for patients with BRAFV600 positive-mutations, respectively, are presented below in

Table 86 and Table 87.

Independent of the BRAF status, the estimated mean overall survival was 5.08 years for patients treated with pembrolizumab and 4.37 years for patients treated with ipilimumab. Patients treated with pembrolizumab accrued 3.14 QALYs compared to 2.69 among patients in the ipilimumab cohort. A table presenting a comparison of the clinical outputs estimated by the model and those obtained from the KEYNOTE-006 clinical trial is presented in Table 89.

Among patients with $BRAF^{V600}$ positive mutations, the estimated mean OS was 3.41 years with dabrafenib and 2.74 years with vemurafenib. Patients treated with pembrolizumab accrued 3.14 QALYs compared to 2.69 among patients in the ipilimumab cohort. A comparison of the clinical outputs estimated by the model and those obtained from the clinical trials is presented in Table 89.

5.7.2 Base-case incremental cost effectiveness analysis results

Table 86 and Table 87 below present the base case incremental cost-effectiveness results for comparisons of pembrolizumab and its relevant comparators in patients with $BRAF^{V600}$ wild type and $BRAF^{V600}$ positive mutations, respectively, incorporating our PAS. It should be noted that these results include our proposed PAS and have been conducted considering the list price for the relevant comparators (given the lack of information publicly available regarding the agreed PAS for each of the comparators). A comparison of the ICERs obtained from pairwise comparisons between pembrolizumab vs. ipilimumab, vemurafenib and dabrafenib taking into account our proposed PAS for pembrolizumab, and considering a range of potential simple discounts to reflect the potential PAS for the comparators is presented in Table 88 below.

Among patients with $BRAF^{V600}$ wild type mutations the results show pembrolizumab to be a dominant strategy compared to ipilimumab, since it results in higher QALYs at a lower average cost per patient (£76,689 for pembrolizumab vs. £97,873 for ipilimumab). As can be seen, considering a 30-year time horizon pembrolizumab resulted in 0.44 additional QALYs with a cost saving of £21,185.

For patients with $BRAF^{V600}$ positive mutations vemurafenib is dominated by pembrolizumab and dabrafenib, while ipilimumab is dominated by pembrolizumab. The number of QALYs gained with pembrolizumab when compared to dabrafenib is 0.97 QALYs, at an additional cost per QALY gained of £5,852.

As shown by the base case results, pembrolizumab is a highly cost-effective therapy even when considering a wide range of possible discounts for the relevant comparators at the

usual ICER thresholds accepted by NICE (see Table 88). Pembrolizumab results in an ICER of either £20,000 or £30,000 per QALY gained when the following discounts apply to the relevant comparators:

- When compared to ipilimumab: 42.3% or 48.5%, respectively.
- When compared to vemurafenib: 57.1% or 80.1%, respectively.
- When compared to dabrafenib: 30.3% or 51.7%, respectively.

Table 86: Base-case results for patients with BRAF^{V600} wild type mutations (discounted, with PAS for pembrolizumab, and considering the list price for the comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline* (QALYs)	ICER (£) incremental (QALYs)
Pembrolizumab	£76,689	5.08	3.14	-	-	-	-	-
Ipilimumab	£97,873	4.37	2.69	£21,185	-0.71	-0.44	Dominated	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

**Baseline = ipilimumab.*

Table 87: Base-case results for patients with BRAF^{V600} positive mutations (discounted, with PAS for pembrolizumab, and considering the list price for the comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline* (QALYs)	ICER (£) incremental (QALYs)
Dabrafenib	£71,029	3.41	2.17	-	-	-	-	-
Pembrolizumab	£76,689	5.08	3.14	£5,660	1.67	0.97	£5,852	£5,852
Vemurafenib	£83,384	2.74	1.73	£6,695	-2.34	-1.40	Dominated	Dominated
Ipilimumab	£97,873	4.37	2.69	£21,185	-0.71	-0.44	£51,336	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

** Baseline = Dabrafenib.*

Table 88: ICERs from the pairwise comparisons for pembrolizumab vs. ipilimumab, vemurafenib and dabrafenib (discounted, with PAS for pembrolizumab, and considering a range of potential simple discounts for the comparators)

Discounts	ICERs for pembrolizumab vs. ipilimumab*	ICERs for pembrolizumab vs. vemurafenib**	ICERs for pembrolizumab vs. dabrafenib**
0%	Dominant	Dominant	£5,852
5%	Dominant	Dominant	£8,188
10%	Dominant	Dominant	£10,524
15%	Dominant	£1,742	£12,861
20%	Dominant	£3,912	£15,197
25%	Dominant	£6,082	£17,533
30%	£336	£8,253	£19,870
35%	£8,339	£10,423	£22,206
40%	£16,341	£12,594	£24,542
45%	£24,344	£14,764	£26,879
50%	£32,347	£16,935	£29,215
55%	£40,349	£19,105	£31,551
60%	£48,352	£21,276	£33,888
65%	£56,355	£23,446	£36,224
70%	£64,357	£25,617	£38,560
75%	£72,360	£27,787	£40,897
80%	£80,363	£29,958	£43,233
85%	£88,365	£32,128	£45,569
90%	£96,368	£34,299	£47,906
95%	£104,371	£36,469	£50,242

*For all patients ($BRAF^{V600}$ wild type and $BRAF^{V600}$ mutation-positive patients)
**For patients with $BRAF^{V600}$ positive mutations

Pembrolizumab qualifies as an end-of-life therapy with an innovative nature (see Section 2.5). For this type of therapies NICE may consider ICERs of around £50,000 per QALY gained. For pembrolizumab to present ICERs lower than this threshold of £50,000 per QALY, the simple discounts for ipilimumab and dabrafenib would need to be equal or lower than 61.03% and 94.48%, respectively. Independent of the discount applied to vemurafenib the ICER when compared to vemurafenib will not reach this threshold. Therefore, applying the end-of-life criteria to pembrolizumab in the submission demonstrates that compared with other therapies used at this point in the patient treatment paradigm, pembrolizumab is a highly cost-effective first line therapy for the treatment of patients with unresectable or metastatic melanoma previously untreated with ipilimumab.

5.7.3 Clinical outcomes from the model

The outcomes of pembrolizumab,[18] ipilimumab,[18] vemurafenib[8;101] and dabrafenib[30;96] reported in the relevant clinical trials have been compared to the outcomes from the model in Table 89. The percentage of patients who had not progressed at 6 months was similar between the trial and the model for all treatments, suggesting that in the short term the outcomes from the model are valid. For dabrafenib and vemurafenib, the estimated median PFS is also similar to that observed from the clinical trials.[8;30;96;101]

Table 89: Comparison of model and trial outcomes

	Pembrolizumab		Ipilimumab		Vemurafenib		Dabrafenib	
Outcome	**Robert *et al.* (2015)[18]**	**Model result**	**Robert *et al.* (2015)[18]**	**Model result**	**McArthur *et al.* (2014)[8]**	**Model result**	**Hauschild *et al.* (2012)/Grob *et al.* (2014)[30;96]**	**Model result**
Median PFS (months)	4.10	5.06	2.80	2.99	6.90	6.90	5.10	5.29
% patients with PFS at 6 months	46.40%	46.71%	26.50%	27.14%	58.00%*	58.00%	47.00%*	47.00%

Key: PFS, progression-free survival.
*Based on digitized data from the PFS Kaplan-Meier plot

5.7.4 Markov traces

Figure 31 and Figure 32 below illustrate how patients (independent of their BRAF status) move through the model states over time when treated with pembrolizumab and ipilimumab, respectively. For patients with $BRAF^{V600}$ positive mutations, the Markov traces related to treatment with dabrafenib and vemurafenib are presented in Figure 33 and Figure 34, respectively. The diagrams show that patients spend longer in the pre-progression health state on pembrolizumab compared to the other treatments and they also experience a longer OS.

Figure 31: Markov trace for pembrolizumab for all patients (independent of BRAF status)

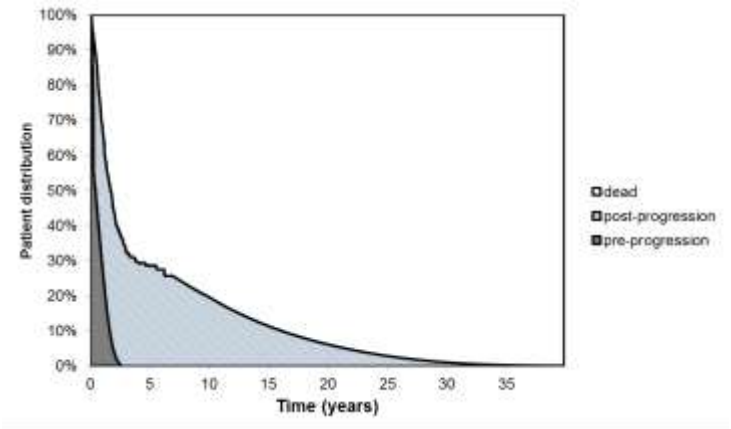


Figure 32: Markov trace for ipilimumab for all patients (independent of BRAF status)

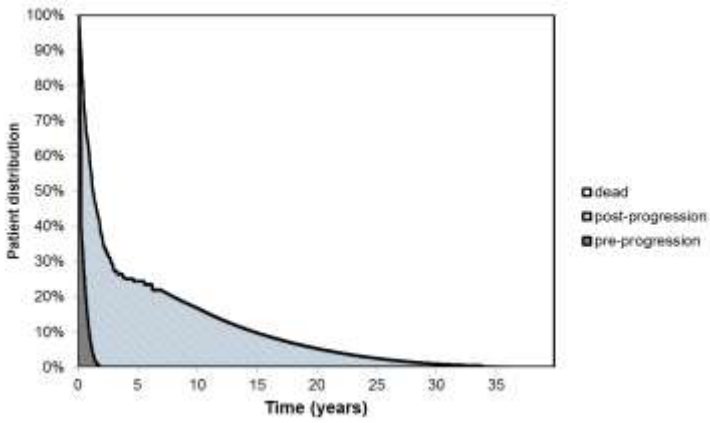


Figure 33: Markov trace for dabrafenib for patients with BRAF^{V600} positive mutations

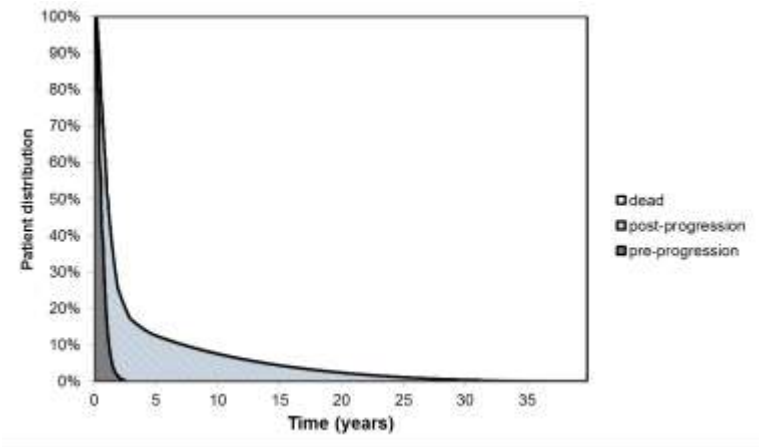
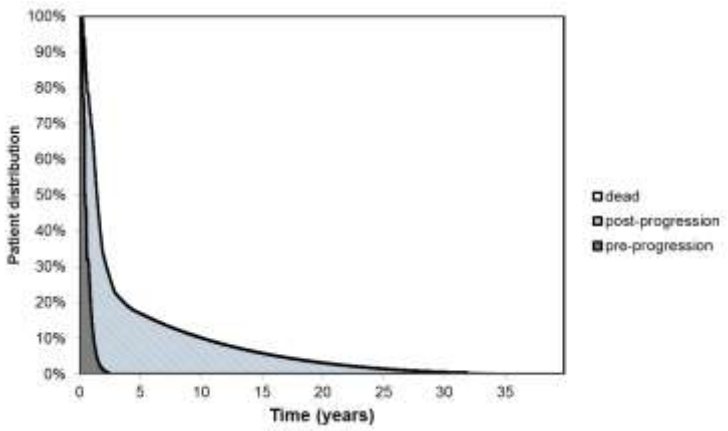


Figure 34: Markov trace for vemurafenib for patients with BRAF^{V600} positive mutations



5.7.5 Accruement of costs, QALYs and LYs over time

Figure 35, Figure 36 and Figure 37 shows how the costs, QALYs and life years accumulate over time, respectively, for patients with $BRAF^{V600}$ wild type mutations treated with pembrolizumab and ipilimumab. For patients with $BRAF^{V600}$ positive mutations treated with pembrolizumab, ipilimumab, vemurafenib or dabrafenib similar information is reported in Figure 38, Figure 39 and Figure 40, respectively. In the base case QALYs are accrued over time according to the time to death of patients, as previously reported (see sections 5.2.2 and 5.4).

Figure 35: Cumulative costs over time for patients with $BRAF^{V600}$ wild type mutations treated with either pembrolizumab or ipilimumab

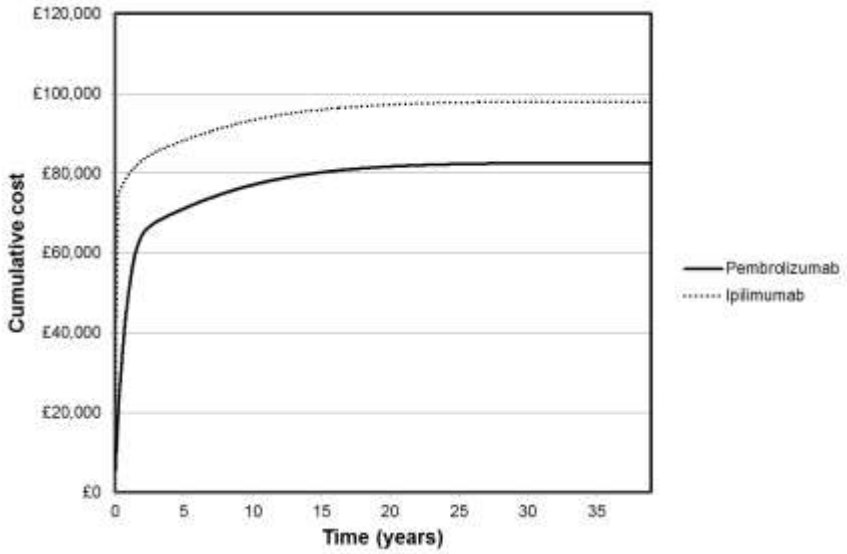
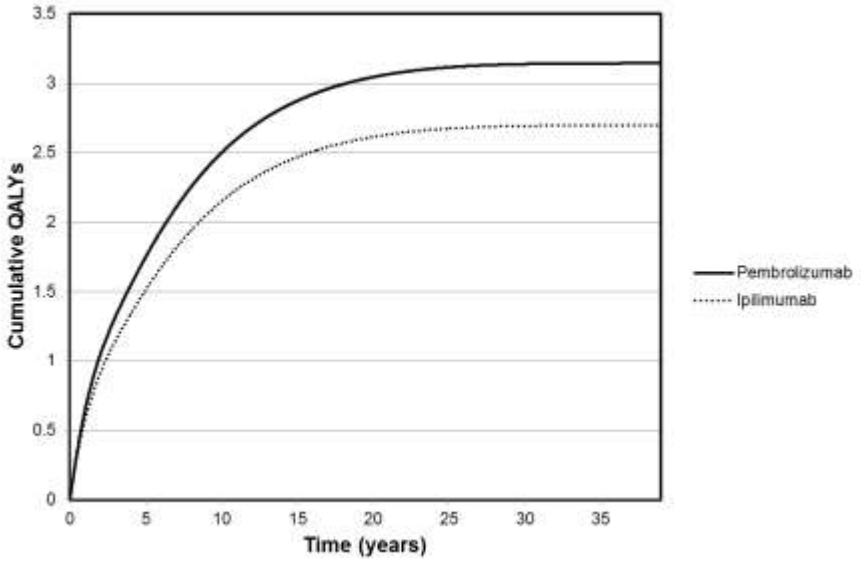
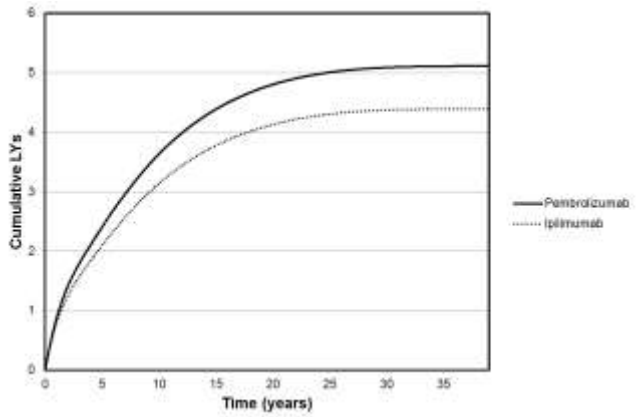


Figure 36: Cumulative QALYs over time for patients with $BRAF^{V600}$ wild type mutations treated with either pembrolizumab or ipilimumab



Key: *QALY, quality-adjusted life year.*

Figure 37: Cumulative LYs over time for patients with BRAF^{V600} wild type mutations treated with either pembrolizumab or ipilimumab



Key: *LY, life year.*

Figure 38: Cumulative costs over time for patients with BRAF^{V600} positive mutations treated with pembrolizumab, ipilimumab, vemurafenib or dabrafenib

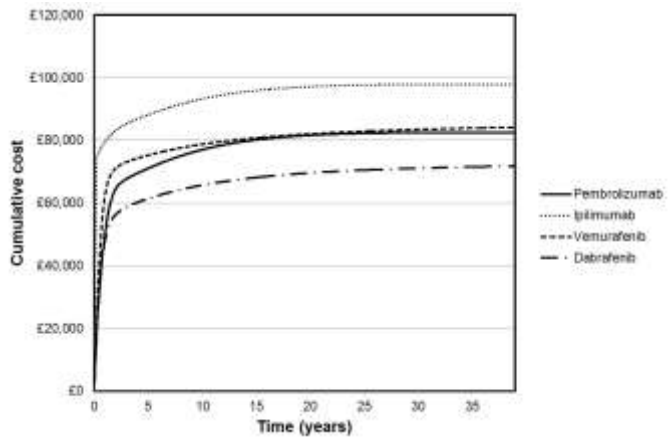
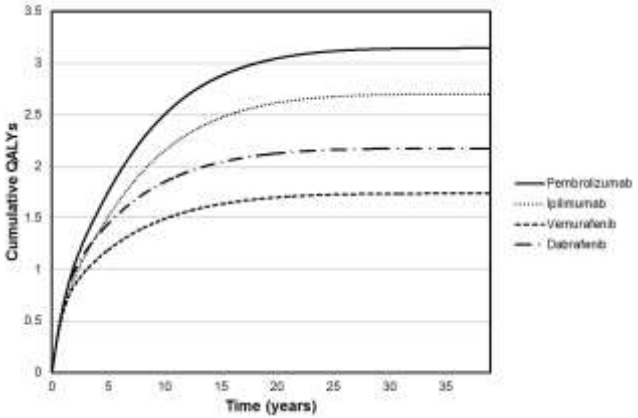
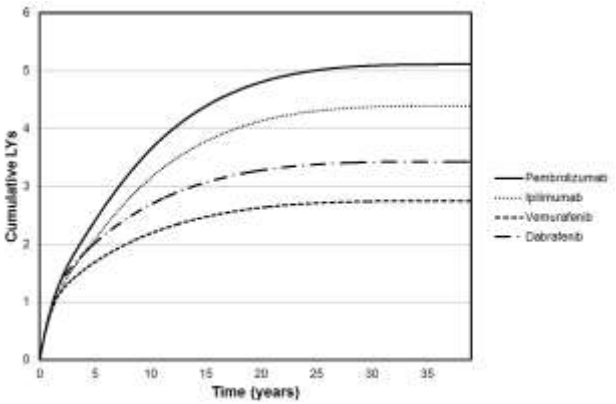


Figure 39: Cumulative QALYs over time Cumulative costs over time for patients with BRAF^{V600} positive mutations treated with pembrolizumab, ipilimumab, vemurafenib or dabrafenib



Key: *QALY, quality-adjusted life year.*

Figure 40: Cumulative LYs over time Cumulative costs over time for patients with BRAF^{V600} positive mutations treated with pembrolizumab, ipilimumab, vemurafenib or dabrafenib



Key: *LY, life year.*

5.7.6 Disaggregated results of the base case incremental cost effectiveness analysis

Table 90 shows the disaggregated life years by health state for patients treated with pembrolizumab or ipilimumab independent of their BRAF status. This shows that patients on pembrolizumab spend longer in both the pre and post-progression health states compared to patients receiving ipilimumab.

Table 90: Disaggregated life-years by health state for pairwise comparisons between pembrolizumab and ipilimumab independent of BRAF status

	Pembrolizumab	Ipilimumab	Incremental
Pre-progression	0.68	0.39	0.29
Post-progression	4.40	3.98	0.42
Total	5.08	4.37	0.71

For patients presenting $BRAF^{V600}$ positive mutations, the disaggregated life years by health state for pairwise comparisons between pembrolizumab and vemurafenib, and between pembrolizumab and dabrafenib, are presented in Table 91 and Table 92, respectively. $BRAF^{V600}$ mutation-positive patients treated with pembrolizumab spend longer in both the pre- and post-progression health states compared to patients receiving either vemurafenib or dabrafenib.

Table 91: Disaggregated life-years by health state for pairwise comparisons between pembrolizumab and vemurafenib for patients with $BRAF^{V600}$ positive mutations

	Pembrolizumab	Vemurafenib	Incremental
Pre-progression	0.68	0.65	0.03
Post-progression	4.40	2.09	2.31
Total	5.08	2.74	2.34

Table 92: Disaggregated life-years by health state for pairwise comparisons between pembrolizumab and dabrafenib for patients with $BRAF^{V600}$ positive mutations

	Pembrolizumab	Dabrafenib	Incremental
Pre-progression	0.68	0.60	0.08
Post-progression	4.40	2.82	1.58
Total	5.08	3.41	1.66

Table 93: Summary of predicted resource use by category of cost for pairwise comparisons of pembrolizumab and ipilimumab independent of BRAF status (including our proposed PAS for pembrolizumab and considering the list price for ipilimumab)

	Pembrolizumab	Ipilimumab	Incremental	Absolute increment	% absolute increment
Treatment Costs	£46,644	£71,113	-£24,469	£24,469	88%
Admin Costs	£3,425	£1,860	£1,565	£1,565	6%
Resource use	£26,576	£24,794	£1,782	£1,782	6%
Adverse events	£44	£106	-£62	£62	0%
Total	£76,689	£97,873	-£21,185	£27,878	100%

Table 94: Summary of predicted resource use by category of cost for pairwise comparisons of pembrolizumab and vemurafenib for patients with $BRAF^{V600}$ positive mutations (including our proposed PAS for pembrolizumab and considering the list price for vemurafenib)

	Pembrolizumab	Vemurafenib	Incremental	Absolute increment	% absolute increment
Treatment Costs	£46,644	£60,929	-£14,286	£14,286	54%
Admin Costs	£3,425	£5,636	-£2,211	£2,211	8%
Resource use	£26,576	£16,735	£9,841	£9,841	37%
Adverse events	£44	£83	-£39	£39	0%
Total	£76,689	£83,384	-£6,695	£26,377	100%

Table 95: Summary of predicted resource use by category of cost for pairwise comparisons of pembrolizumab and dabrafenib for patients with $BRAF^{V600}$ positive mutations (including our proposed PAS for pembrolizumab and considering the list price for dabrafenib)

	Pembrolizumab	Dabrafenib	Incremental	Absolute increment	% absolute increment
Treatment Costs	£46,644	£45,195	£1,449	£1,449	14%
Admin Costs	£3,425	£5,814	-£2,389	£2,389	23%
Resource use	£26,576	£19,910	£6,666	£6,666	63%
Adverse events	£44	£110	-£66	£66	1%
Total	£76,689	£71,029	£5,660	£10,570	100%

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix 22.

For unresectable or metastatic melanoma patients previously untreated with ipilimumab and with BRAF^{V600} wild type mutations

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis considering BRAF^{V600} wild type patients are presented in Table 96. These results incorporate our proposed PAS for pembrolizumab and the list price for ipilimumab. There is variation in the results both in terms of QALYs and costs between the two treatment arms compared to the base case, with ipilimumab becoming a dominated option as part of the PSA results.

Table 96: Incremental cost-effectiveness results based on PSA among patients with BRAF^{V600} wild type mutations (discounted, with PAS for pembrolizumab and at list price for ipilimumab, vemurafenib and dabrafenib)

	Total Costs	Total QALYs	Incremental costs	Incremental QALYS	ICER
Pembrolizumab	£87,685	3.12	£9,954	-0.45	Dominated
Ipilimumab	£97,639	2.67			

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The scatterplot of PSA iterations (see Figure 45) shows that there is some overlap in terms of the costs and QALYs for pembrolizumab and ipilimumab. However, the costs for ipilimumab are generally higher and the number of QALYs gained is lower. For pembrolizumab there are a small number of iterations which resulted in much higher costs than the range within which the rest of the simulations lie. This is due to the large amount of uncertainty in the PFS extrapolation using the Gompertz curve fit to the KEYNOTE-006 trial data. At extreme probabilities the amount of time spent in PFS increases significantly. Given that patients are assumed to receive pembrolizumab until progression this results in higher costs as patients receive pembrolizumab for much longer. This is further illustrated below, where we have run a scenario analysis where pembrolizumab treatment is limited to a maximum of 2 years (see Figure 45) where we do not see these outliers. This does not have as much of an impact for ipilimumab since it has a maximum of four doses which are all received in the first 12 weeks of the model. Therefore, ipilimumab treatment costs are not affected by longer PFS in the longer-term.

The cost-effectiveness acceptability curve shows that there is an approximately 89.9% chance of pembrolizumab to be cost-effective when compared to ipilimumab at the £20,000 per QALY threshold, 90.5% when we consider a thresholds of £30,000, and 91.6% at a threshold of £50,000 per additional QALY gained.

Figure 41: Scatterplot of PSA results among patients with BRAF^{V600} wild type mutations (1,000 simulations; results discounted, with PAS for pembrolizumab and at list price for ipilimumab)

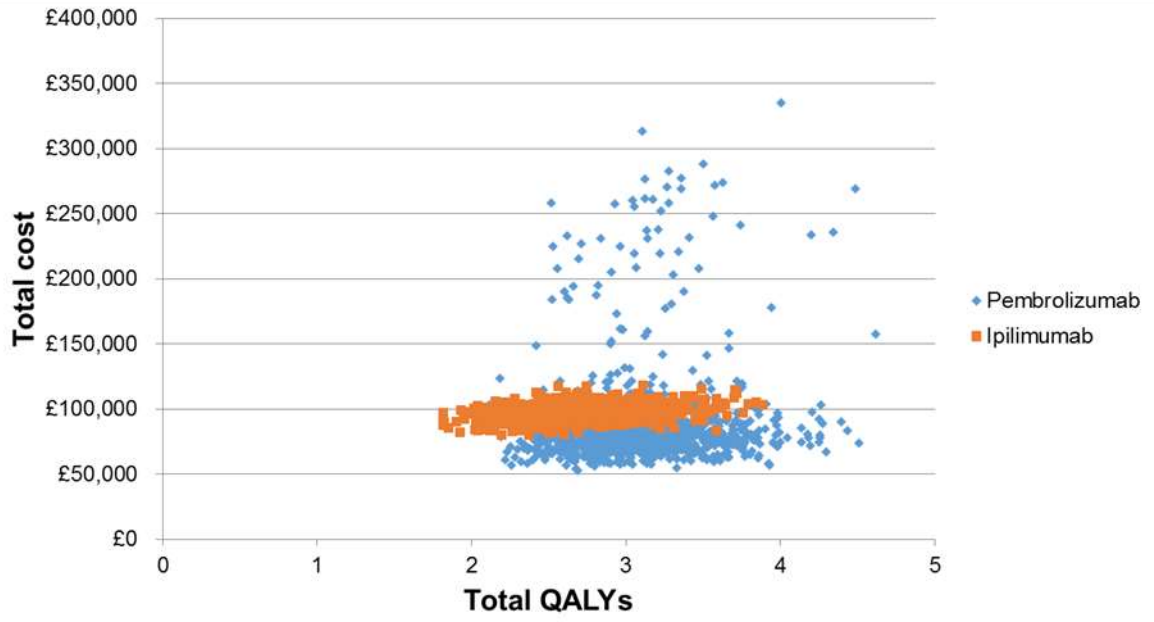
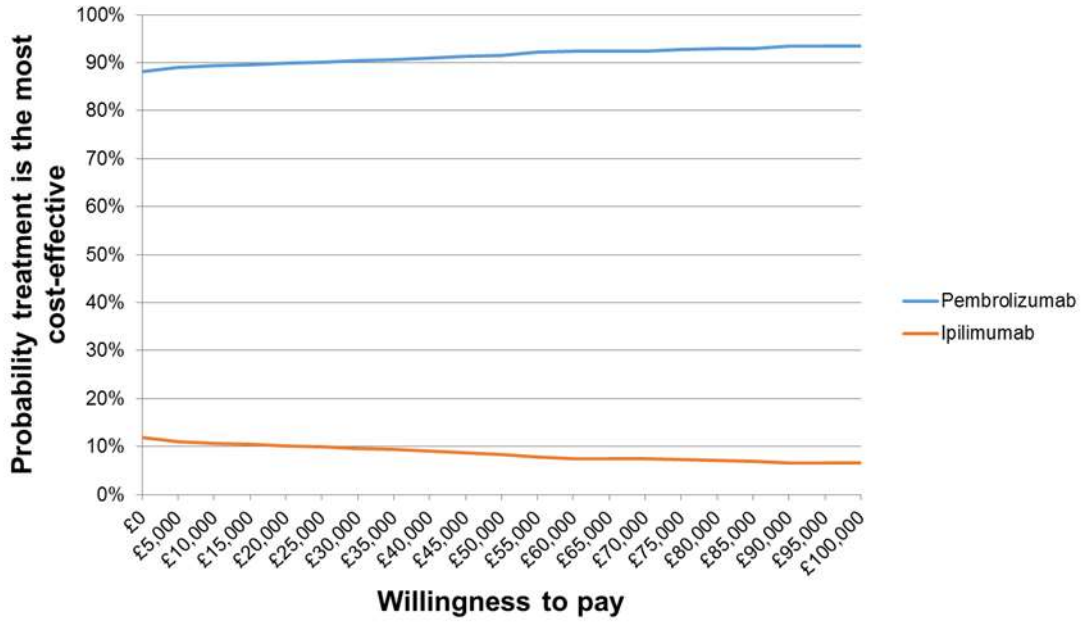


Figure 42: Cost-effectiveness acceptability curve among patients with BRAF^{V600} wild type mutations (results discounted, with PAS for pembrolizumab and at list price for ipilimumab)



For unresectable or metastatic melanoma patients previously untreated with ipilimumab and with BRAF^{V600} positive mutations

The incremental cost-effectiveness results obtained from the PSA when considering BRAF^{V600} mutation-positive patients are presented in Table 97. These results incorporate our proposed PAS for pembrolizumab and the list price for vemurafenib and dabrafenib. There is

variation in the results both in terms of QALYs and costs between the two treatment arms compared to the base case, with ipilimumab becoming a dominated option as part of the PSA results.

Table 97: Incremental cost-effectiveness results based on PSA among patients with BRAF^{V600} positive mutations (discounted, with PAS)

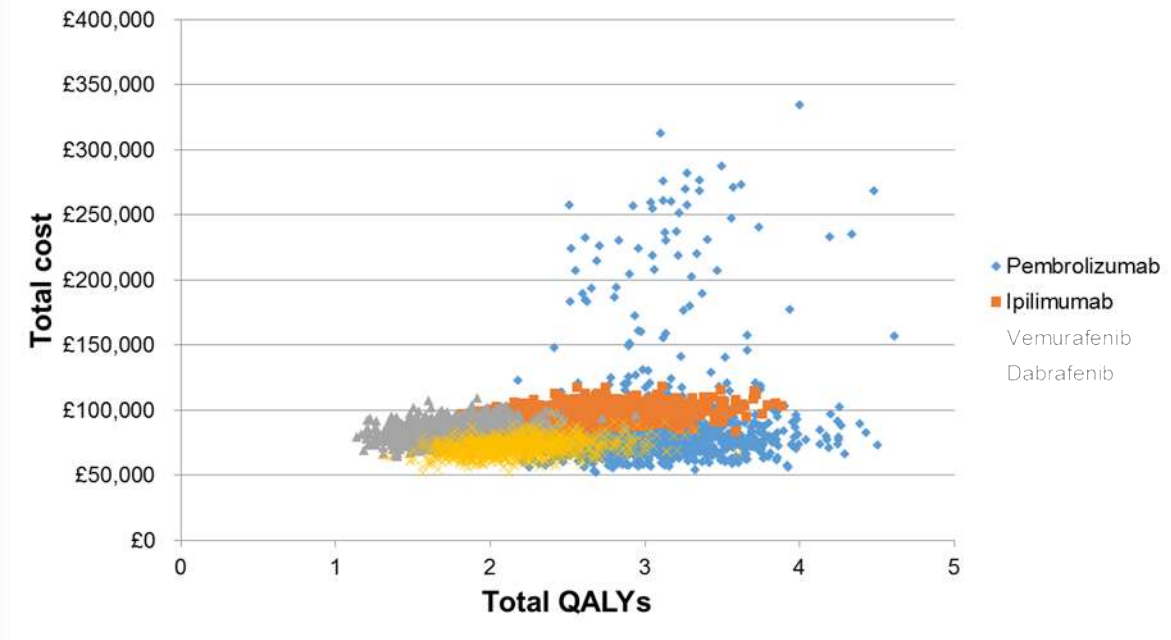
Technologies	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	ICER (£) incremental (QALYs)
Dabrafenib	£71,602	2.19	-	-	-	-
Vemurafenib	£83,939	1.74	£12,338	-0.44	Dominated	Dominated
Pembrolizumab	£87,685	3.12	£16,083	0.93	£17,234	£17,234
Ipilimumab	£97,639	2.67	£9,954	-0.45	£53,525	Dominated

The probabilistic mean ICER is significantly greater than the deterministic mean. As seen with the previous PSA on BRAF^{V600} wild type patients, this is due to the uncertainty associated with the short-term PFS data from the KEYNOTE-006 clinical trial. In some samples a substantial proportion of patients are being treated for a very long time. Based on discussions with clinical experts, it is unlikely that patients surviving in the long term will be treated for life. In the KEYNOTE-006 trial, treatment with pembrolizumab was to be continued until the patients had completed 24 months of treatment with pembrolizumab.[18] On the basis of this protocol-driven maximum duration of therapy, we decided that the PSA should be re-run, assuming that patients in the progression-free health state would stop treatment after 2 years, as this provides information about the impact of duration of therapy. The results are presented in Figure 47.

As can be seen in the scatter plot of PSA iterations (see Figure 43), a small number of iterations resulted in much higher costs due to the uncertainty surround the extrapolation of PFS. We did not see these outliers when we limited treatment with pembrolizumab to a maximum of 2 years (Figure 47).

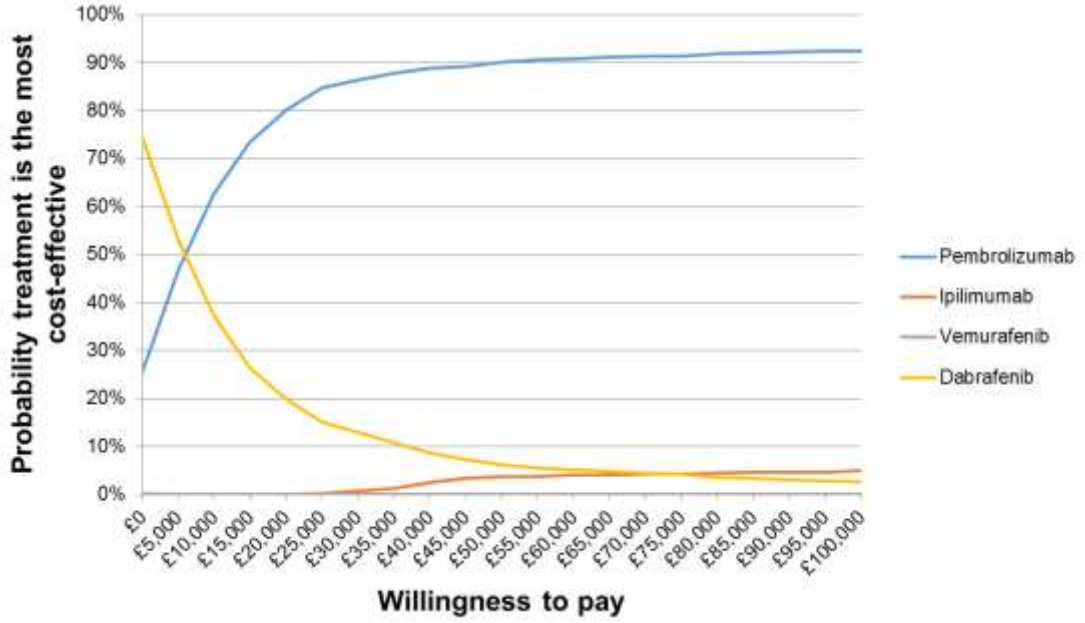
The cost-effectiveness acceptability curves show that there is an approximately 80.1% chance of pembrolizumab to be cost-effective against ipilimumab, vemurafenib and dabrafenib at a £20,000 per QALY threshold. When thresholds of £30,000 and £50,000 per QALY are considered, this chance increases to 86.4% and 90.1%, respectively.

Figure 43: Scatterplot of PSA results among patients with BRAF^{V600} positive mutations (1,000 simulations; results discounted, with PAS for pembrolizumab and at list price for ipilimumab, vemurafenib and dabrafenib)



Key: *QALY, quality-adjusted life year.*

Figure 44: Cost-effectiveness acceptability curve among patients with BRAF^{V600} positive mutations (results discounted, with PAS for pembrolizumab and at list price for ipilimumab, vemurafenib and dabrafenib)



PSA considering a maximum duration of therapy of 2 years for pembrolizumab

For unresectable or metastatic melanoma patients previously untreated with ipilimumab and with $BRAF^{V600}$ wild type mutations

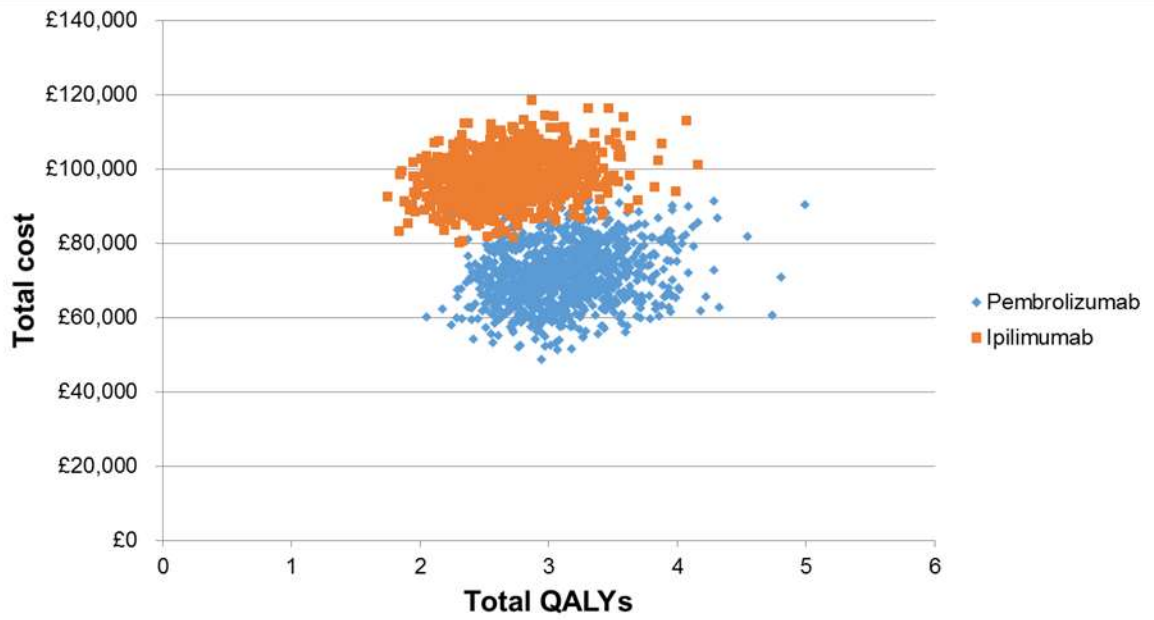
In the protocol of the KEYNOTE-006 trial, patients remained on treatment until confirmed progression, the onset of unacceptable side effects, a decision from the clinician or the patient to withdraw treatment or up to 24 months of therapy.[18] To provide additional information we opted to replicate the trial design in relation to maximum duration of therapy in the probabilistic sensitivity analysis. The results of these analyses are presented in Table 98 and Table 99, and Figure 45 to Figure 48.

Table 98: Incremental cost-effectiveness results based on deterministic results and PSA among patients with $BRAF^{V600}$ wild type mutations (discounted, with PAS for pembrolizumab and at list price for ipilimumab) considering a maximum duration of treatment therapy of 2 years

	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Deterministic results					
Pembrolizumab	£70,982	3.14	£26,891	-0.44	Dominated
Ipilimumab	£97,874	2.69			
Probabilistic results					
Pembrolizumab	£71,265	3.12	£26,526	-0.44	Dominated
Ipilimumab	£97,791	2.67			
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

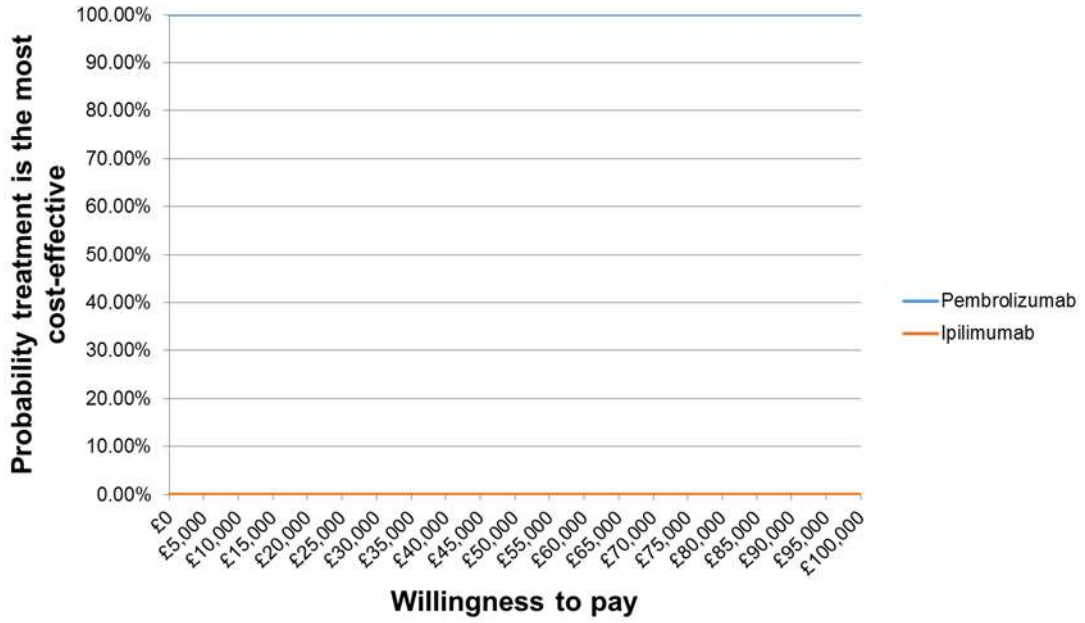
When a maximum duration of therapy of 2 years is considered the probabilistic mean ICER, the incremental costs and the incremental QALYs are close to the deterministic results. This shows that the higher probabilistic mean ICER value and the large spread around the costs seen in Figure 41 are driven by responding patients receiving drug treatment for life. The associated scatterplot shows less variation around the simulated ICERs (see Figure 45) and the cost-effectiveness acceptability curve under this scenario shows that there is 100% chance of pembrolizumab being cost-effective when compared to BSC at the £50,000 per QALY threshold (see Figure 46)

Figure 45: Scatterplot of PSA results among patients with BRAF^{V600} wild type mutations (1,000 simulations; results discounted, with PAS for pembrolizumab and at list price for ipilimumab, vemurafenib and dabrafenib) considering a maximum duration of therapy of 2 years



Key: *QALY, quality-adjusted life year.*

Figure 46: Cost-effectiveness acceptability curve among patients with BRAF^{V600} wild type mutations (results discounted, with PAS for pembrolizumab and at list price for ipilimumab, vemurafenib and dabrafenib) considering a maximum duration of therapy of 2 years



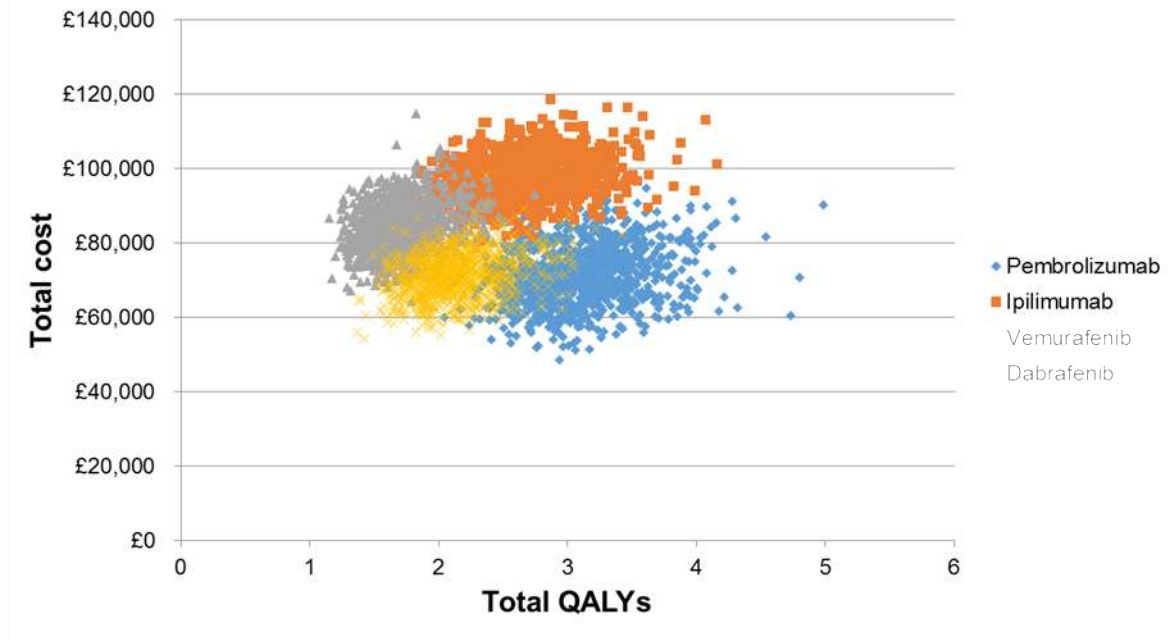
For unresectable or metastatic melanoma patients previously untreated with ipilimumab and with BRAF^{V600} positive mutations

Table 99: Incremental cost-effectiveness results based on PSA among patients with BRAF^{V600} positive mutations (discounted, with PAS) considering a maximum duration of therapy of 2 years

Technologies	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	ICER (£) incremental (QALYs)
Deterministic results						
Pembrolizumab	£70,983	3.14	-	-	-	-
Dabrafenib	£71,029	2.17	£46	-0.97	Dominated	Dominated
Vemurafenib	£83,384	1.73	£12,401	-1.40	Dominated	Dominated
Ipilimumab	£97,874	2.69	£26,891	-0.44	Dominated	Dominated
Probabilistic results						
Pembrolizumab	£71,265	3.12	-	-	-	-
Dabrafenib	£71,365	2.15	£101	-0.97	Dominated	Dominated
Vemurafenib	£83,920	1.71	£12,655	-1.40	Dominated	Dominated
Ipilimumab	£97,791	2.67	£26,526	-0.44	Dominated	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

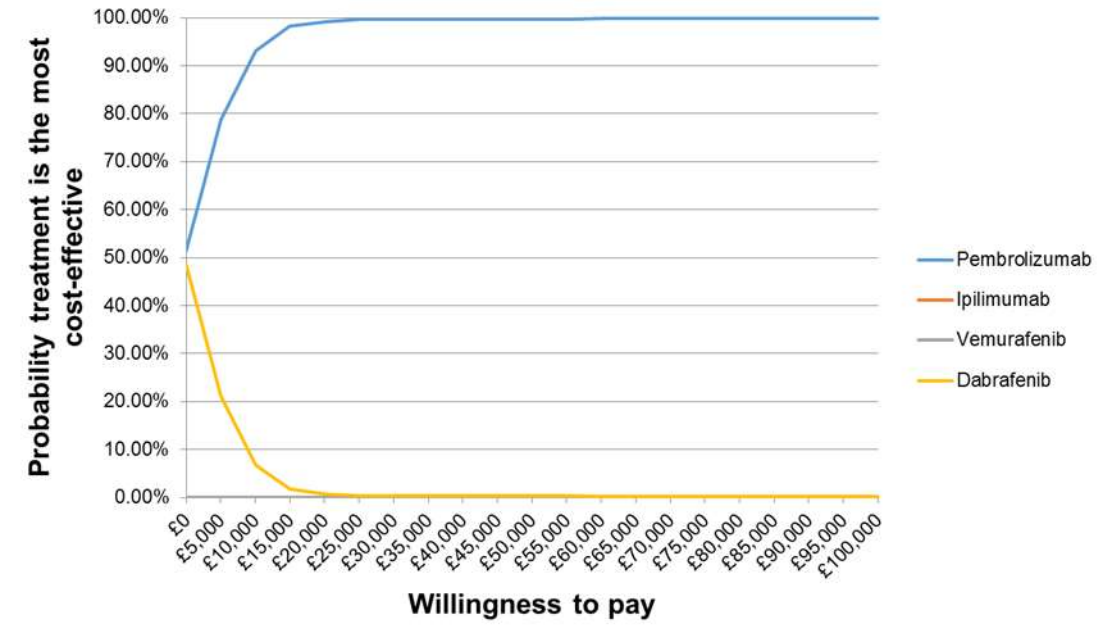
When a maximum duration of therapy of 2 years was considered to run an additional PSA on the subpopulation of BRAF^{V600} mutation positive patients, the probabilistic mean ICER, incremental costs and incremental QALYs were close to the deterministic result (see Table 99). This shows that the higher probabilistic mean ICER value and the large spread around the costs seen are driven by responding patients receiving drug treatment for life. The associated scatterplot shows less variation around the simulated ICERs (see Figure 47) and the cost-effectiveness acceptability curve under this scenario shows that there is 99.7% chance of pembrolizumab being cost-effective when compared to BSC at the £50,000 per QALY threshold (see Figure 48).

Figure 47: Scatterplot of PSA results among patients with BRAF^{V600} positive mutations (1,000 simulations; results discounted, with PAS for pembrolizumab and at list price for ipilimumab, vemurafenib and dabrafenib) considering a maximum duration of therapy of 2 years



Key: *QALY, quality-adjusted life year.*

Figure 48: Cost-effectiveness acceptability curve among patients with BRAF^{V600} positive mutations (results discounted, with PAS for pembrolizumab and at list price for ipilimumab, vemurafenib and dabrafenib) considering a maximum duration of therapy of 2 years



5.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted for the following key variables using the 5% and 95% confidence intervals for the variables except when it is indicated otherwise:

- Baseline characteristics (including proportion of males/females by weight category)

- Administration costs
- Resource utilization
- Proportion of patients actually receiving the expected dose
- Costs of terminal care
- Proportion of patients experiencing AEs
- Costs of AEs
- Time-to-death utilities
- PFS and OS extrapolation curve parameters

The results of the deterministic sensitivity analyses for pairwise comparisons with ipilimumab, vemurafenib and dabrafenib are presented in Figure 49, Figure 50 and Figure 51, respectively. These are presented with the PAS for pembrolizumab and at list price for the comparator treatments since the PAS discounts for these treatments are unknown. Tornado diagrams varying the PAS discount applied to ipilimumab, vemurafenib and dabrafenib are presented in Appendix 28.

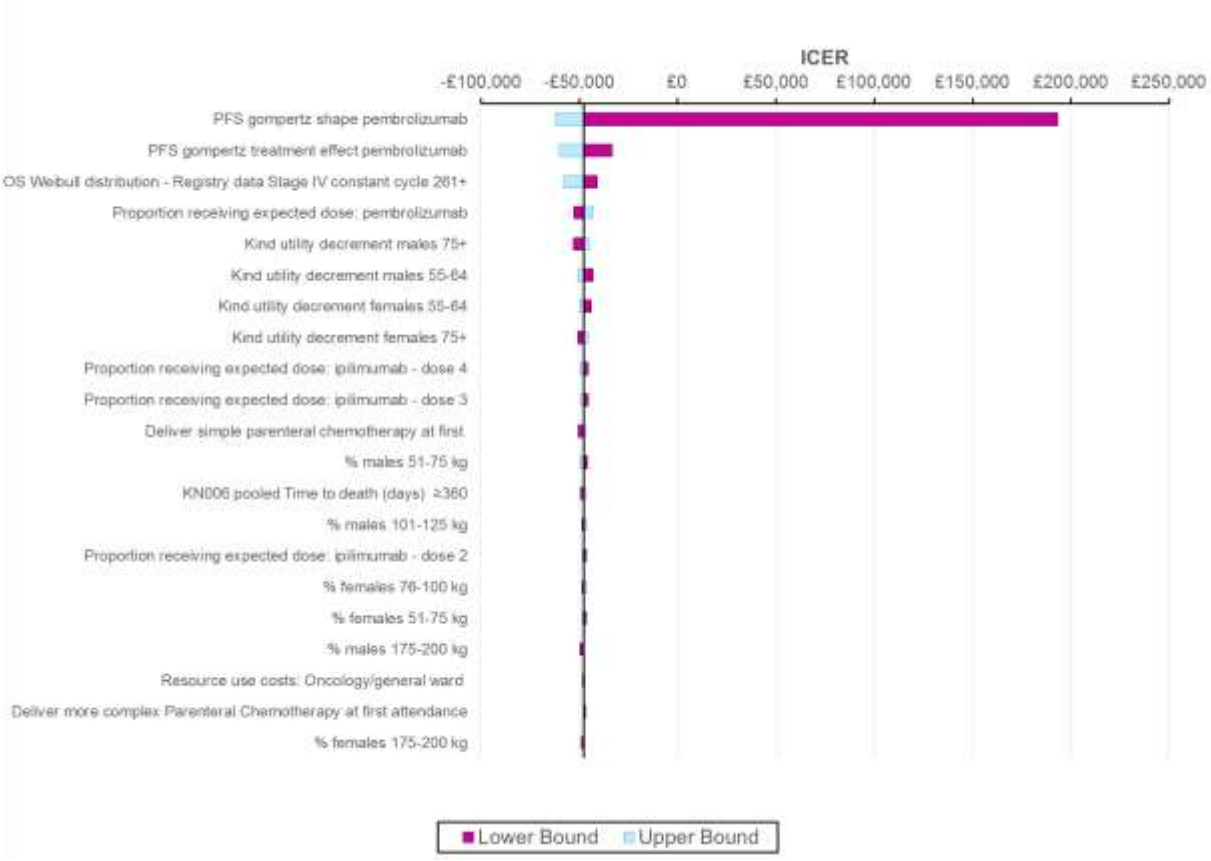
In the comparison with ipilimumab (Figure 49), the inputs that most affects the ICER are the curve fit parameters assumed for pembrolizumab PFS, as the majority of the benefits associated with pembrolizumab come from increased survival over ipilimumab. This further supports the interpretation of the outliers in the probabilistic results (Figure 41 and Figure 43), that the uncertainty around the PFS extrapolation parameters caused some simulations to result in very high costs for pembrolizumab. The other variables that significantly affected the ICER were the parameters for OS extrapolation using the data from Balch (2001)[88] and the proportion of pembrolizumab patients receiving their expected dose. The rest of the modified variables had a minor impact on the estimated ICER.

In the comparison with vemurafenib (Figure 50), the inputs that most affect the ICER are the curve fit parameters assumed for pembrolizumab PFS, as the majority of the benefits associated with pembrolizumab come from increased survival over vemurafenib. The other variables that significantly affected the ICER were the monthly risk of progression for the extrapolation of vemurafenib PFS, the monthly mortality risk for the extrapolation of vemurafenib OS, parameters for OS extrapolation using the data from Balch (2001)[88] and

the proportion of pembrolizumab patients receiving their expected dose. The rest of the modified variables had a minor impact on the estimated ICER.

In the comparison with dabrafenib (Figure 51), the inputs that most affect the ICER are the curve fit parameters assumed for pembrolizumab PFS, since the majority of the benefits associated with pembrolizumab come from increased survival over dabrafenib. Other variables that significantly affected the ICER are the monthly risk of progression for the extrapolation of vemurafenib PFS (since the extrapolation for dabrafenib was assumed to be the same as for vemurafenib) and the proportion of pembrolizumab patients receiving their expected dose. The rest of the modified variables had a minor impact on the estimated ICER.

Figure 49: Tornado diagram presenting the results of the deterministic sensitivity analysis versus ipilimumab for the 20 most sensitive variables (discounted results, with PAS for pembrolizumab, ipilimumab at list price)*

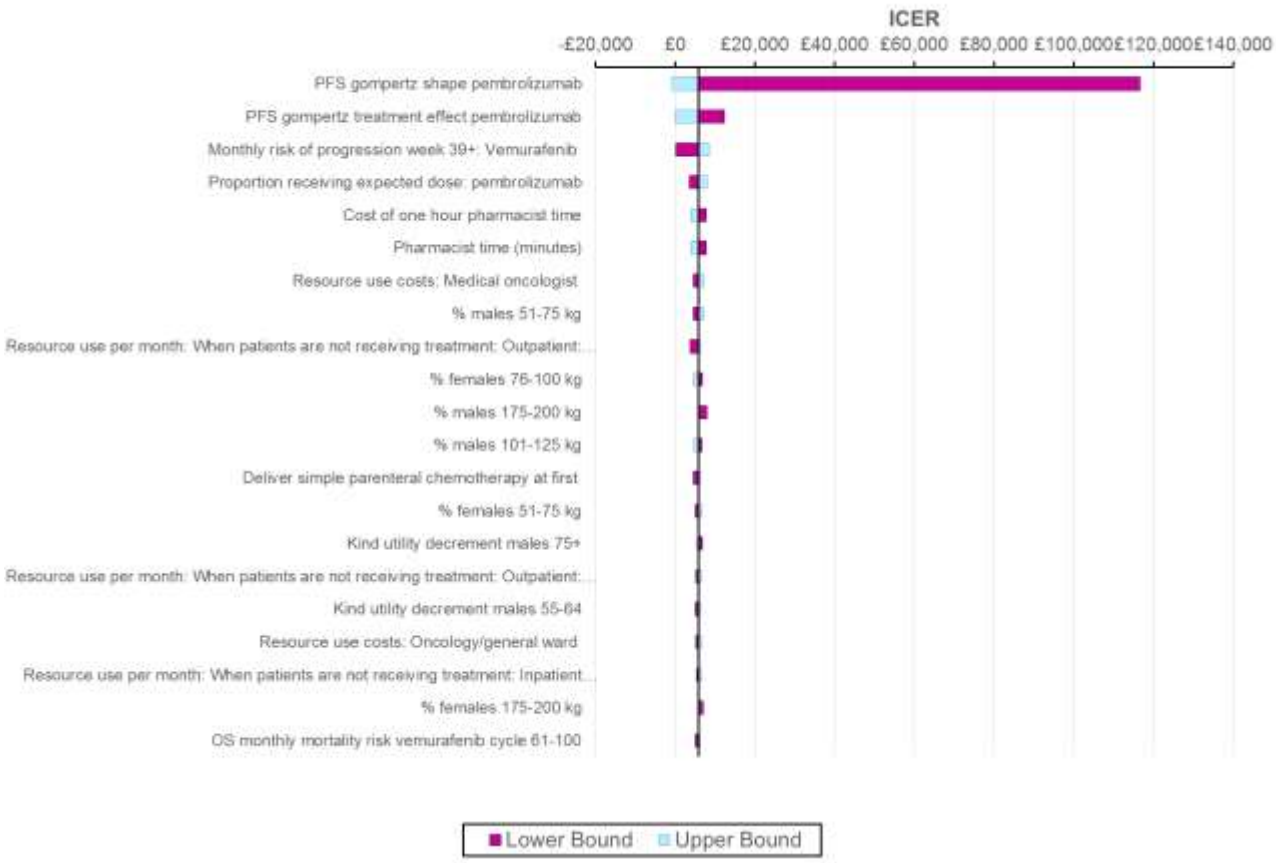


Key: *ICER, incremental cost-effectiveness ratio; kg, kilogram; PFS, progression-free survival; OS, overall survival*
Notes: **Negative ICER indicates that pembrolizumab is the dominant treatment.*

Figure 50: Tornado diagram presenting the results of the deterministic sensitivity analysis versus vemurafenib for the 20 most sensitive variables (discounted results, with PAS for pembrolizumab, vemurafenib at list price)

Key: *ICER, incremental cost-effectiveness ratio; kg, kilogram; PFS, progression-free survival; OS, overall survival*

Figure 51: Tornado diagram presenting the results of the deterministic sensitivity analysis versus dabrafenib for the 20 most sensitive variables (discounted results, with PAS for pembrolizumab, dabrafenib at list price)



Key: *ICER, incremental cost-effectiveness ratio; kg, kilogram; PFS, progression-free survival; OS, overall survival*

5.8.3 Scenario analyses

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions. Including:

- Alternative extrapolation scenarios to estimate PFS and long-term OS for pembrolizumab and the comparators were tested (these scenarios form Scenarios 1 to 16 which are described in detail in Section 5.3.3. and are listed in Table 70).
- Applying the HR observed in ipilimumab naïve patients in the KEYNOTE-001 trial for the efficacy of pembrolizumab 2mg/kg Q3W compared with pembrolizumab 10mg/kg Q3W (scenario 17)
- Applying the HR for the OS of pembrolizumab compared with ipilimumab observed in the KEYNOTE-006 trial to the long-term extrapolation (Schadendorf data; scenario 18)

- Using the algorithm from TA319 to adjust OS KM data for other trials relative to KEYNOTE-006 characteristics (scenario 19)
- Varying the time horizon of the model
    - 10 years (scenario 20)
    - 20 years (scenario 21)
    - 40 years (scenario 22)
- Changing the source of time to death utilities (using ipilimumab first-line submission data; scenario 23)
- Utilities based on progression status
    - Based on KEYNOTE-006 data (scenario 24)
    - Based on Batty et al. (2011)[114] (scenario 25)
- Removing the age-adjustment for utilities (scenario 26)
- Assessing the impact of vial sharing in clinical practice (scenario 27)
- Using alternative methodologies to calculate the cost of terminal care
    - Georghiou & Bardsley[134] cost applied as a weekly cost in the final 90 days of life (scenario 28)
    - Addicott & Dewar[135] cost applied as a weekly cost in the final 90 days of life (scenario 29)
- Restricting pembrolizumab use to a maximum of 2 years (scenario 30)
- Adjusting PFS Km data as well as OS data
    - Using the Korn algorithm (scenario 31)
    - Using the TA319 algorithm (scenario 32)
- Not discounting the results (scenario 33)

The results of scenario analyses are shown in Table 100 for the $BRAF^{V600}$ mutation wild-type population. These demonstrate that if the ipilimumab simple discount is up to 40%, pembrolizumab remains cost-effective at a willingness to pay threshold of £20,000 per QALY gained for all scenarios but one (see Table 100). If the willingness to pay threshold is £30,000 per QALY gained, pembrolizumab remains cost-effective compared with ipilimumab in all scenarios up to a discount of 45% on the price of ipilimumab. Pembrolizumab remains cost-effective compared with ipilimumab up to a discount of 55% to the price of ipilimumab when the willingness to pay threshold is £50,000 per QALY gained, as applied to drugs meeting end-of-life criteria (see Table 64).

The results of scenario analyses for the $BRAF^{V600}$ mutation positive population are shown in Table 101 for the comparator treatments at list price. Table 101 shows the impact of scenario analyses when the comparator treatments are at list price, and demonstrates that scenarios 8-11 have the biggest impact on the results of the analysis. In these scenarios pembrolizumab is no longer considered the most cost-effective treatment. These four results represent scenarios in which OS for pembrolizumab and ipilimumab are modelled using the log-normal curve fit to the KEYNOTE-006 clinical trial data. As discussed in section 5.3.3, the curves fit to the KEYNOTE-006 data were not clinically plausible in the long-term, as long-term survival for ipilimumab was projected below what would be expected with ipilimumab based on published data.[9]

Scenario analysis results are shown in Appendix 29 to show the impact of a range of potential simple discounts to ipilimumab, vemurafenib and dabrafenib prices. The range of potential simple discounts includes variations from 15% to 95% in 5% increments. In the majority of these scenarios pembrolizumab remains the most cost-effective treatment at a willingness to pay threshold of £20,000 per QALY gained up to a 40% discount to ipilimumab, vemurafenib and dabrafenib. If the willingness to pay threshold is £30,000 per QALY gained pembrolizumab remains the most cost-effective treatment in most of the scenarios up to a discount of 45% to the price of ipilimumab, vemurafenib and dabrafenib. Even with a discount of 60% to the price of ipilimumab, vemurafenib and dabrafenib, pembrolizumab is still a cost-effective treatment in the majority of scenarios when the willingness to pay threshold is £50,000 per QALY gained, which is the usual accepted threshold for end-of-life therapies like pembrolizumab.

Table 100: Results from the scenario analyses for unresectable or metastatic melanoma patients previously untreated with ipilimumab and with $BRAF^{V600}$ wild type mutations

Scenario	ICER: Pembrolizumab vs ipilimumab (varying discount for ipilimumab)									
	List price	5%	10%	15%	20%	25%	30%	35%	40%	45%
Base case	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£336	£8,339	£16,341	£24,344
1	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£354	£8,356	£16,359	£24,361
2	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£657	£8,271	£15,885	£23,499
3	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£677	£8,291	£15,904	£23,518
4	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£1,415	£4,492	£7,569	£10,647	£13,724
5	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£1,422	£4,499	£7,577	£10,654	£13,731
6	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£1,940	£4,741	£7,542	£10,343	£13,144
7	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£1,946	£4,746	£7,547	£10,348	£13,149
8	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£8,353	£17,513	£26,674
9	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£8,383	£17,543	£26,703
10	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£8,393	£17,914	£27,434
11	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£8,424	£17,944	£27,464
12	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£2,995	£6,960	£10,925	£14,889	£18,854
13	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£2,898	£7,063	£11,229	£15,394	£19,560
14	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£3,462	£7,725	£11,988	£16,252
15	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£2,996	£7,353	£11,711	£16,068	£20,425
16	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£336	£8,339	£16,341	£24,344

Scenario	ICER: Pembrolizumab vs ipilimumab (varying discount for ipilimumab)									
	List price	5%	10%	15%	20%	25%	30%	35%	40%	45%
17	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£138	£5,551	£10,965	£16,378	£21,791	£27,204
18	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£1,501	£4,540	£7,579	£10,618	£13,657
19	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£336	£8,339	£16,341	£24,344
20	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£8,293	£18,605	£28,917
21	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£27	£8,318	£16,610	£24,902
22	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£361	£8,343	£16,325	£24,307
23	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£306	£7,598	£14,890	£22,182
24	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£361	£8,958	£17,555	£26,153
25	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£347	£8,603	£16,860	£25,117
26	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£327	£8,107	£15,887	£23,667
27	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£5,301	£11,887	£18,474	£25,061
28	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£7,954	£15,956	£23,959
29	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£6,752	£14,754	£22,757
30	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£3,497	£11,500
31	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£336	£8,339	£16,341	£24,344
32	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£336	£8,339	£16,341	£24,344
33	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	Ipilimumab dominated	£2,591	£9,001	£15,411	£21,821
Scenario	ICER: Pembrolizumab vs ipilimumab (varying PAS for ipilimumab)									
	50%	55%	60%	65%	70%	75%	80%	85%	90%	95%
Base case	£32,347	£40,349	£48,352	£56,355	£64,357	£72,360	£80,363	£88,365	£96,368	£104,371
1	£32,364	£40,366	£48,368	£56,371	£64,373	£72,376	£80,378	£88,380	£96,383	£104,385

Scenario	ICER: Pembrolizumab vs ipilimumab (varying PAS for ipilimumab)									
	50%	55%	60%	65%	70%	75%	80%	85%	90%	95%
2	£31,114	£38,728	£46,342	£53,956	£61,570	£69,184	£76,799	£84,413	£92,027	£99,641
3	£31,132	£38,746	£46,360	£53,974	£61,588	£69,202	£76,815	£84,429	£92,043	£99,657
4	£16,801	£19,879	£22,956	£26,034	£29,111	£32,188	£35,266	£38,343	£41,420	£44,498
5	£16,808	£19,886	£22,963	£26,040	£29,117	£32,195	£35,272	£38,349	£41,427	£44,504
6	£15,944	£18,745	£21,546	£24,347	£27,148	£29,949	£32,750	£35,550	£38,351	£41,152
7	£15,949	£18,750	£21,551	£24,352	£27,152	£29,953	£32,754	£35,555	£38,356	£41,156
8	£35,835	£44,996	£54,156	£63,317	£72,478	£81,639	£90,799	£99,960	£109,121	£118,282
9	£35,863	£45,024	£54,184	£63,344	£72,505	£81,665	£90,825	£99,986	£109,146	£118,306
10	£36,955	£46,475	£55,996	£65,516	£75,037	£84,557	£94,078	£103,598	£113,119	£122,640
11	£36,984	£46,504	£56,024	£65,544	£75,064	£84,584	£94,105	£103,625	£113,145	£122,665
12	£22,819	£26,783	£30,748	£34,712	£38,677	£42,642	£46,606	£50,571	£54,536	£58,500
13	£23,726	£27,891	£32,057	£36,222	£40,388	£44,554	£48,719	£52,885	£57,050	£61,216
14	£20,515	£24,778	£29,041	£33,305	£37,568	£41,831	£46,094	£50,357	£54,621	£58,884
15	£24,782	£29,140	£33,497	£37,854	£42,212	£46,569	£50,926	£55,283	£59,641	£63,998
16	£32,347	£40,349	£48,352	£56,355	£64,357	£72,360	£80,363	£88,365	£96,368	£104,371
17	£32,617	£38,030	£43,443	£48,856	£54,269	£59,682	£65,095	£70,508	£75,921	£81,334
18	£16,696	£19,735	£22,775	£25,814	£28,853	£31,892	£34,931	£37,970	£41,009	£44,048
19	£32,347	£40,349	£48,352	£56,355	£64,357	£72,360	£80,363	£88,365	£96,368	£104,371
20	£39,229	£49,541	£59,853	£70,165	£80,477	£90,789	£101,101	£111,413	£121,725	£132,037
21	£33,193	£41,485	£49,776	£58,068	£66,360	£74,651	£82,943	£91,235	£99,526	£107,818
22	£32,289	£40,271	£48,253	£56,235	£64,217	£72,199	£80,181	£88,163	£96,145	£104,127
23	£29,474	£36,766	£44,058	£51,349	£58,641	£65,933	£73,225	£80,517	£87,809	£95,101
24	£34,750	£43,347	£51,944	£60,542	£69,139	£77,736	£86,333	£94,931	£103,528	£112,125
25	£33,374	£41,631	£49,888	£58,144	£66,401	£74,658	£82,915	£91,172	£99,429	£107,686
26	£31,447	£39,227	£47,008	£54,788	£62,568	£70,348	£78,128	£85,908	£93,689	£101,469
27	£31,648	£38,235	£44,821	£51,408	£57,995	£64,582	£71,168	£77,755	£84,342	£90,929
28	£31,962	£39,964	£47,967	£55,970	£63,972	£71,975	£79,978	£87,980	£95,983	£103,986
29	£30,760	£38,762	£46,765	£54,768	£62,770	£70,773	£78,776	£86,779	£94,781	£102,784
30	£19,503	£27,505	£35,508	£43,511	£51,513	£59,516	£67,519	£75,522	£83,524	£91,527
31	£32,347	£40,349	£48,352	£56,355	£64,357	£72,360	£80,363	£88,365	£96,368	£104,371
32	£32,347	£40,349	£48,352	£56,355	£64,357	£72,360	£80,363	£88,365	£96,368	£104,371
33	£28,231	£34,641	£41,051	£47,461	£53,871	£60,281	£66,691	£73,101	£79,511	£85,921

Table 101: Incremental results from the scenario analysis (PAS included for pembrolizumab, list price for ipilimumab, vemurafenib and dabrafenib) for unresectable or metastatic melanoma patients previously untreated with ipilimumab and with BRAF^{V600} positive mutations

	ICER (incremental analysis)			
Scenario	Pembrolizumab	Ipilimumab	Vemurafenib	Dabrafenib
Base case	£5,852	Dominated	Dominated	-
1	£5,852	Dominated	Dominated	-
2	£6,046	Dominated	Dominated	-
3	£6,046	Dominated	Dominated	-
4	£6,284	Dominated	Dominated	-
5	£6,284	Dominated	Dominated	-
6	£6,278	Dominated	Dominated	-
7	£6,278	Dominated	Dominated	-
8	-	Dominated	Dominated	£8,826
9	-	Dominated	Dominated	£8,826
10	-	Dominated	Dominated	£8,826
11	-	Dominated	Dominated	£8,826
12	-	Dominated	Dominated	Dominated
13	£6,509	Dominated	Dominated	-
14	£5,556	Dominated	Dominated	-
15	£4,475	Dominated	Dominated	-
16	£3,869	Dominated	Dominated	-
17	£10,776	Dominated	Dominated	-
18	£6,393	Dominated	Dominated	-
19	£5,841	Dominated	Dominated	-
20	£8,591	Dominated	Dominated	-
21	£6,869	Dominated	Dominated	-
22	£5,081	Dominated	Dominated	-
23	£5,438	Dominated	Dominated	-
24	£6,906	Dominated	Dominated	-
25	£6,374	Dominated	Dominated	-
26	£5,630	Dominated	Dominated	-
27	-	Dominated	Dominated	Dominated
28	£1,877	Dominated	Dominated	-
29	£3,257	Dominated	Dominated	-
30	-	Dominated	Dominated	Dominated
31	£6,471	Dominated	Dominated	-
32	£6,272	Dominated	Dominated	-
33	£4,528	Dominated	Dominated	-

Key: *ICER, incremental cost-effectiveness ratio.*

5.8.4 Summary of sensitivity analyses results

The probability of pembrolizumab being cost effective in BRAF^{V600} wild type patients at a £20,000 per QALY threshold is 89.9% compared to ipilimumab, and 80.1% against ipilimumab, vemurafenib and dabrafenib in BRAF^{V600} mutation positive patients. When a cost-effectiveness threshold of £30,000 is considered, the probability of pembrolizumab being cost-effective is 90.5% against ipilimumab in BRAF^{V600} wild type patients, and 86.4%

against ipilimumab, vemurafenib and dabrafenib in $BRAFV^{600}$ mutation positive patients. The probabilistic results when considering a maximum duration of therapy of 2 years give a more realistic estimate and shows the probabilistic mean to be close to the base case ICER.

One-way sensitivity analysis showed the curve parameters associated with pembrolizumab PFS (Gompertz curve) to have the greatest impact on the ICER. The parameters used to extrapolate OS in the long-term also had an impact, but this was much smaller.

Scenario analysis showed that the cost-effectiveness of pembrolizumab is robust to the majority of potential sources of uncertainty. The scenario analysis showed that the only scenarios which resulted in pembrolizumab not being cost-effective were those using the log-normal curves fit to KEYNOTE-006 trial data for OS. These scenarios were unrealistic as long-term survival for ipilimumab was projected below what would be expected with ipilimumab based on published data.[9]

5.9 Subgroup analysis

No subgroup analyses were considered in the cost-effectiveness analysis.

One of the secondary outcomes of the KEYNOTE-006 study[23] was to evaluate OS, PFS, and ORR in the biomarker positive subgroup defined by programmed cell death 1 ligand (PDL1) expression level receiving either MK-3475 or ipilimumab.

Analyses of PFS, ORR, and OS in PD-L1 positive and PD-L1 negative subgroups show that efficacy is slightly greater in PD-L1 positive patients, which is consistent with the mechanism of action of an anti-PD-1 agent. However, the benefit of pembrolizumab over ipilimumab was observed in both PD-L1 positive and PD-L1 negative subgroups. Given that the patients eligible for pembrolizumab as for this submission have access to few remaining treatment options that result in limited survival benefit, the clinical utility of this biomarker is questionable for unresectable or metastatic melanoma patients. Moreover, efficacy was consistent across all major demographic and prognostic subgroups including age, sex, ECOG PS, baseline LDH and BRAF status. On this basis, no subgroup analyses were undertaken and therefore no subgroups have been considered in the do novo cost-effectiveness analysis.

5.9.1 Types of subgroups that are not considered relevant

Not applicable as no subgroups analyses were undertaken.

5.9.2 Analysis of subgroups

Not applicable as no subgroups analyses were undertaken.

5.9.3 Definition of the characteristics of patients in the subgroup

Not applicable as no subgroups analyses were undertaken.

5.9.4 Description of how the statistical analysis was carried out

Not applicable as no subgroups analyses were undertaken.

5.9.5 Results of subgroup analyses

Not applicable as no subgroups analyses were undertaken.

5.9.6 Identification of any obvious subgroups that were not considered

Not applicable as no subgroups analyses were undertaken.

5.10 Validation

Validation of de novo cost-effectiveness analysis

5.10.1 Methods used to validate and quality assure the model

Clinical benefit

Comparing the model outcomes to clinical trial outcomes

The outcomes of the pembrolizumab 10mg/kg and ipilimumab arms of the KEYNOTE-006 trial have been compared to the outcomes from the model. For more details comparing the results generating from the model to the outcomes from the model please refer to section 5.7.3.

Expert validation

The model approach and inputs are similar to the model used for the ongoing submission for pembrolizumab in patients previously treated with ipilimumab[22] which has been validated by an external health economist (Dr. Laura Bojke, from the Centre for Health Economics, University of York). This individual was selected as a leading expert in health economics practice and methodology development in the UK and is a regular member of NICE ERG's. The model structure for the ongoing appraisal of pembrolizumab for patients previously treated with ipilimumab[22], the selection of appropriate dataset, the survival analysis undertaken, the assumptions regarding extrapolation and the utility values used were all discussed.

The accuracy of the implementation and programming of the model was verified via internal quality control processes using an internal quality control checklist, available in Appendix 31.

5.11 Interpretation and conclusions of economic evidence

5.11.1 Comparison with published economic literature

No study assessing the cost-effectiveness of pembrolizumab was identified from the systematic literature review. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

5.11.2 Relevance of the economic evaluation for all patient groups

The target population included in the economic evaluation was consistent with the population eligible for pembrolizumab as per the licence. As mentioned previously (see section 5.3.1), the evidence considered for pembrolizumab was mainly derived from the KEYNOTE-006 trial, which assessed a population of patients who were naïve to ipilimumab treatment as expected in the licence.

5.11.3 Generalisability of the analysis to the clinical practice in England

The population included in the KEYNOTE-006 trial, the main source of clinical evidence for pembrolizumab considered in the economic model, was generally comparable with the UK population (see section 4.13.2).

In terms of the treatment pathway, in clinical practice in England $BRAF^{V600}$ wild type patients would receive ipilimumab as first-line treatment, while $BRAF^{V600}$ mutation-positive patients can be treated with either a BRAF agent (vemurafenib or dabrafenib) or ipilimumab. Therefore, patients would receive pembrolizumab as an alternative option to these comparator treatments in line with the expected licence. The economic analysis takes into consideration the above and therefore is relevant to clinical practice.

5.11.4 Strengths and weaknesses of the evaluation

The analysis performed makes use of the best available evidence to inform the model. Head-to-head data from the KEYNOTE-006 trial comparing pembrolizumab to ipilimumab was used in the economic evaluation.
For the extrapolation of the results in the long term, appropriate external sources were used, whenever required, and data from patients previously untreated was prioritised to better reflect the target population.

The main weaknesses associated with this cost-effectiveness analysis are the following:

- OS data:

Due to the lack of long-term OS data for pembrolizumab, alternative ways were identified to extrapolate the benefit of pembrolizumab in the long term. For this, the best available evidence from the trials and from other external sources was used. Some relevant assumptions regarding the impact of pembrolizumab in the long term were required. These assumptions were derived from comparisons of data for pembrolizumab and ipilimumab in previously treated patients, and were validated clinically. The impact of applying these assumptions was tested in sensitivity analyses by taking into account alternative potential scenarios.

- Assumption of proportional hazards:

Proportional hazards for pembrolizumab compared with ipilimumab were assumed to generate the ipilimumab data. In the short-term this assumption was confirmed. In the long-term the assumption of proportional hazards is expected to hold.

- Treatment duration:

There is uncertainty around the treatment duration of pembrolizumab. Patients are expected to be treated until disease progression is confirmed (or discontinuation due to AEs), as for the license. It is unclear whether patients surviving in the long term will be treated for life.

Extensive sensitivity analyses were conducted to inform the uncertainty around the above limitations, which helped understanding what key variables could potentially have a major impact on the cost-effectiveness results.

The results presented demonstrate the cost-effeciveness of pembrolizumab using the NICE accepted threshold of £20,000-£30,000. Applying the end-of-life criteria support the conclusion that within the context of innovative end-of-life therapies pembrolizumab is a cost-effective therapeutic option compared with the use of ipilimumab and, if $BRAF^{V600}$ mutation-positive, with a BRAF or MEK inhibitor.

5.11.5 Further analyses

The evidence base for this economic analysis was derived from the first interim analysis of KEYNOTE-006, with the exception of overall survival which was derived from the second interim analysis. The first interim analysis, which was to be performed after at least 260 patients had progressed or died in all groups and all patients had been followed-up for at least 6 months, had a data cut-off date of 3 September 2014. The second interim analysis, which was to be performed after at least 290 patients had died in all groups and all patients

had been followed-up for at least 9 months or all patients had been followed up for at least 12 months, had a data cut-off date of 3 March 2015.[18]

A final analysis was to be conducted after 435 deaths have been observed, or all patients have been followed up for a minimum of 21 months. However, after reviewing the results of the second interim analysis, the data and safety monitoring committee recommended that results be unblinded and pembrolizumab be made available to patients with disease progression in the ipilimumab group.[18] As OS was positive at IA2, no formal OS analysis will be conducted at the planned final analysis. However, patients will continue to be followed up and long-term survival for this study will be updated as deemed appropriate.

6 Assessment of factors relevant to the NHS and other parties

6.1 Analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness

Not applicable.

6.2 Number of people eligible for treatment in England

The estimated number of incident melanoma cases was calculated by applying the proportion of incidence melanoma cases in England to the total population in England. The number of incident patients are reported in Table 102. The most recent England population estimates and melanoma incidence[137] have been used to calculate the aforementioned estimates.

Table 102: Estimates of incident population

Parameters	Estimate	Source
Total population – England	53,865,800	ONS Mid-2013 UK population estimates[138]
Incidence melanoma - England	0.0211%	Calculated (average of male and female)
	0.0210%	ONS cancer registration 2012 (released June 2014) – male[137]
	0.0212%	ONS cancer registration 2012 (released June 2014) - female[137]
Estimate of incident melanoma population	11,366	Calculated (total population England x average male/female incidence melanoma England)
Proportion of patient with stage IIIc or IV disease	10%	Vemurafenib NICE costing report (NICE costing template TA269)[24]
Estimated number of incident patients stage IIIc-IV eligible for treatment in England in 2012	1,137	Calculated (total population England x average male/female incidence melanoma England x proportion of patient with stage IIIc-IV disease)
Proportion of increase in incidence per annum	3.5%	Decisions resources malignant melanoma June 2006. National Institute for Health and Care Excellence (NICE). Ipilimumab for previously untreated melanoma - manufacturer submission (2013)[139]

The number of expected incident cases of malignant melanoma for 2012 in England is estimated to be 11,366, of whom 1,137 cases (10%) are expected to be stage IIIc and IV. A 3.5% yearly increase was accounted for in the estimation of the number of incident patients eligible for treatment in England in 2016 (i.e. year 1). In 2016, the population (i.e. untreated with ipilimumab) eligible to receive PD-1 treatment is estimated to be 1,304.

The estimated PD-1 class share comes from MSD internal forecasting[140] and has been used to estimate the maximum number of stage IIIc and IV patients eligible for these drugs. Pembrolizumab will be one of a number of drugs in this class available over this forecast period (Table 103).

Table 103: Estimated maximum number of patients stage IIIc and IV treated with PD-1 per year

Based on estimated maximum number of stage IIIc and IV patients treated with PD-1

	2016	2017	2018	2019	2020
Estimated number of patients stage IIIc and IV eligible for treatment with PD-1	**1,304**	**1,350**	**1,397**	**1,446**	**1,497**
Estimated class share - PD-1 class	57%	67%	69%	69%	69%
Estimated maximum number of stage IIIc and IV patients treated with PD-1	**743**	**904**	**964**	**998**	**1,033**

6.3 Assumptions that were made about current treatment options and uptake of technologies

The main assumptions made to estimate the number of eligible patients to receive pembrolizumab treatment are:

- Patients receive the licensed dose of 2mg/kg until disease progression is confirmed.
- The following inputs are based on outcomes from KEYNOTE-006:
    - The mean treatment duration (in cycles), which was obtained from the results of the economic model.
    - The average number of vials per patients (with no vial sharing) used was based on European patient weights (detailed in section 5.5.2).
- All patients have been tested for $BRAF^{V600}$ mutation status[24]
- 0% are treated through clinical trials[24]
- 3.5% incidence change rates per year[3]

6.4 Assumptions that were made about market share in England

We have not formally examined the breakdown of market share between pembrolizumab and the other soon to be approved drugs in this class. Overall market share for the class is based upon MSD forecasting and applied to the maximum number of patients stage IIIc and IV eligible for treatment with PD-1 drugs as explained in section 6.2 and presented in Table 103**Error! Reference source not found.**.[140]

6.5 Other significant costs associated with treatment that may be of interest to commissioners

Technology costs and other significant costs associated with treatment with pembrolizumab are described in section 5.5.

As per SmPC (see Appendix 1) pembrolizumab is administered at a dose of 2mg/kg every 3 weeks until disease progression is confirmed or unacceptable toxicities. As mentioned in section 5 a proportion of patients are predicted to survive for longer than with currently available treatments. Mean overall survival is currently based on extrapolation method and the true mean overall survival observed in the population is not yet known.

In addition, pembrolizumab is administered every 3 weeks, which is lower than compared to some of the available chemotherapies and the administration time required per cycle is shorter than for some other chemotherapies (i.e. 30 minutes instead of 60 minutes or longer).

6.6 Unit costs assumed and how they were calculated

All unit costs considered here estimate the annual budget on the NHS in England and are based upon the ones included in the economic in section 5.5.

The unit cost of one 50mg vial of pembrolizumab is £1,315.

As described in section 5.5 pembrolizumab administrations take less than 30 minutes each. It was therefore assumed and agreed with NHSE when submitting the additional NHSE costs from implementing the EAMS scheme for pembrolizumab for patients with advanced melanoma who have received previous treatment, that the administration cost for pembrolizumab would be the simple parenteral chemotherapy administered as outpatient costs (NHS reference costs 2013/2014 SB12Z: £245.17).[131]

6.7 Estimates of resource savings

The resource savings of introducing pembrolizumab to the market are explained in the results of section 5.7.

6.8 State the estimated annual budget impact on the NHS in England.

Introduction of pembrolizumab in the market in England is expected to displace the use of ipilimumab to subsequent treatment lines. The estimated budget impact on the NHS in England of all PD-1 agents is presented in Table 104. MSD has not attempted to estimate the pembrolizumab share of the PD-1 class, however if it was 50% for the first year, the figure would be half of that shown in the table below (i.e. £18,423,371.50).

Table 104: Estimated budget impact over 5 years

Based on an estimate assuming that the maximum number of stage IIIc and IV patients are all treated with pembrolizumab

	2016	2017	2018	2019	2020
Estimated maximum number of stage IIIc and IV patients treated with pembrolizumab	**743**	**904**	**964**	**998**	**1,033**
Total costs for pembrolizumab	**£49,564**	**£49,564**	**£49,564**	**£49,564**	**£49,564**
Total treatment costs	£46,840	£46,840	£46,840	£46,840	£46,840
Total administration costs	£2,680	£2,680	£2,680	£2,680	£2,680
Total AE costs	£44	£44	£44	£44	£44
Maximum budget impact with pembrolizumab	**£36,846,742**	**£44,826,971**	**£47,780,868**	**£49,453,198**	**£51,184,060**

6.9 Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

No other quantifiable resource savings or redirection of resources is expected.

6.10 Highlight the main limitations within the budget impact analysis.

The maximum estimated budget impact with pembrolizumab was calculated based on the maximum number of stage IIIc and IV patients treated with pembrolizumab. As with all NICE submisisons it has not been possible to include the benefit to society of patients returning to work.

7 References

(1) KEYNOTE-006: Phase III study of pembrolizumab (MK-3475) versus ipilimumab in patients with ipilimumab-naive advanced melanoma. Paper presented at: American Association for Cancer Research (AACR) Annual Meeting 2015; 18-22 April, 2015; United States of America, Philadelphia. 2015.

(2) National Institute for Health and Care Excellence (NICE). Single Technology Appraisal for ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). https://www nice org uk/guidance/ta268 [Accessed on: 10/02/2015] 2012

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Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

Dear [redacted],

The Evidence Review Group (ERG), Liverpool Reviews & Implementation Group (LRiG), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 29 May 2015 by Merck Sharp & Dohme. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some aspects of 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 3 July 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 queries related to this letter, please contact [redacted], Project Manager [redacted] in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on clinical effectiveness data

Clinical-effectiveness data:

A1. If available, please provide a copy of the European Medicine Agency (EMA) EPAR for pembrolizumab. If the EPAR is not available, please provide a detailed rationale for the use of the 2mg/kg dose (licensed dose) rather than the 10mg/kg dose (KEYNOTE-006) for the patient population considered in this appraisal.

Statistical methods:

A2. Regarding the final analysis of KEYNOTE-006, it is stated on page 65 of the company submission:

"Since patients in the ipilimumab arm were expected to discontinue treatment earlier compared to patients in the pembrolizumab arms, and patients who discontinued ipilimumab were likely to receive other PD-1 treatments similar to pembrolizumab after discontinuation….The 95% confidence intervals for the HR for OS before or after proper adjustment of the cross-over effect will be provided at the final analysis (therefore not of relevance to IA1 and IA2 results)".

However, it is then stated on page 87 of the company submission:

"As OS was positive at IA2, no formal OS analysis will be conducted at the planned final analysis. However, patients will continue to be followed up and long-term survival for this study will be updated as deemed appropriate."

a. Please clarify why this final analysis will not be performed; without this analysis, the impact of crossover to other treatments appears to not have been properly adjusted for in the results presented for IA1 and IA2.

b. Please provide a list of other treatments received by patients in the KEYNOTE-006 trial following discontinuation.

A3. Tables 22, 24, 26, 27, and 29 of the company submission present two-sided p-values based on the log-rank test for comparisons between pembrolizumab 10 mg/kg Q2W and pembrolizumab 10 mg/kg Q3W. Please clarify whether this two-sided hypothesis testing was pre-specified for KEYNOTE-006.

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A4. Please clarify how the range was obtained for response duration in Table 31 of the company submission. It is unclear as the median has not been reached but the range is given.

A5. For the sample size calculation for KEYNOTE-006 described on page 63 of the company submission, please provide the parameters used for the exponential distribution. Please also confirm that the power to demonstrate superiority used for the sample size calculation is 85%.

A6. Page 167 of the company submission states that the Schoenfeld residual test was used to test the assumption of proportional hazards.

a. Please confirm whether the proportional hazards assumption for progression-free survival was assessed for the complete trial period or only for the first 12 weeks.

b. Please confirm whether the Schoenfeld residuals method was also used for testing proportional hazards for the primary analysis of overall survival.

c. Please confirm whether the Schoenfeld residuals method was pre-specified for the testing of the proportional hazards assumption.

d. Please clarify what is meant by the 'non-parametric Kaplan-Meier method' which is specified in the clinical study report to be used for the analysis of progression-free survival.

A7. Please provide justification for why one-sided hypothesis testing has been used for KEYNOTE-006. It is common practice for phase III trials to use two-sided hypothesis testing. Please also justify why the sample size calculation was carried out using a one-sided p-value as the sample size is likely to be smaller as a result of using a one-sided hypothesis test.

A8. Please provide the p-values for the tests for interaction for the subgroup analyses presented in Figures 14–17 of the company submission.

A9. Table 37 of the company submission provides results for key efficacy endpoints for KEYNOTE-006; both arms are labelled as pembrolizumab 10 mg/kg Q3W. Please provide an updated table in order to indicate which results are for the pembrolizumab 10 mg/kg Q3W arm, and which are for the pembrolizumab 2 mg/kg arm.

A10. On page 111 of the company submission, it is stated that "KEYNOTE-006 first-line subgroup has 0%; KEYNOTE-006 second-line subgroup has 100%". Please clarify what is meant by this statement given that in the network meta-analysis network of

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evidence (company submission, pages 112–113) it is shown that KEYNOTE-006 includes both first- and second-line patients.

A11. Please provide further information as to why the Weibull model was chosen as the most appropriate survival model for the network meta-analysis. Specifically, please provide a list of the survival models used for the network meta-analysis, results of the assessments of goodness of fit for each of these models, and further explanation as to why the Weibull provided "plausible extrapolation of relative treatment effects beyond the trial follow-periods available" (company submission, page 121).

Section B: Clarification on cost-effectiveness data

B1. Please explain the treatment pathway for patients who were allocated to the ipilimumab arm of the KEYNOTE-006 trial but withdrew from the trial before receiving a single dose of ipilimumab. Please also explain precisely how such patients have been accounted for in the analyses.

B2. Please provide the following Kaplan-Meier analyses (listed in a. to e. below) to the following specification:

Population: The per protocol population, including all patients lost to follow-up or withdrawing from the trial.

Censoring: Censor lost to follow-up and withdrawn patients at the time recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, and not when last seen. Please use the format of the table provided below.

Trial data set: KEYNOTE-006, latest data cut.

a. Time to death from any cause (overall survival) Kaplan-Meier analysis for both of the pembrolizumab 10 mg/kg treatment arms (Q2W and Q3W) separately and combined (3 analyses)

b. Time to death from any cause (overall survival) Kaplan-Meier analysis for the ipilimumab arm (1 analysis)

c. Time from disease progression by investigator assessment to death from any cause (post-progression survival) Kaplan-Meier analysis for the pembrolizumab arms (both arms separately and combined) and the ipilimumab arm (4 analyses)

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d. Time to treatment discontinuation Kaplan-Meier analysis for both pembrolizumab arms (separately and combined) and the ipilimumab arm (4 analyses)

e. Time to progression by investigator assessment (progression-free survival) Kaplan-Meier analysis for patients with BRAFV600 mutation positive disease for both pembrolizumab arms (separately and combined) and the ipilimumab arm, split by those who did / did not receive a BRAF inhibitor prior to commencing the trial (8 analyses).

Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

B3. Please provide a table summarising the baseline characteristics as shown in Table 17 of the company submission, together with the time since initial diagnosis of malignant melanoma (mean and range) of patients in the KEYNOTE-006 trial for the three subgroups: ‘pembrolizumab treated (both regimens)’, ‘ipilimumab treated’ and ‘ipilimumab untreated’.

B4. Please provide a table showing the baseline age-sex distribution of patients in the KEYNOTE-006 trial in 5 year age bands (under 20 years, 20–24 years, 25–29 years, etc.), for patients in the both pembrolizumab arms jointly and separately, and for the ipilimumab arm.

B5. Please provide results for EQ-5D scores in the KEYNOTE-006 trial split between US and non-US patients for the company submission Appendix 30, Table 17, Table 18,

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Table 20 (but with progression by INV not IRO assessment) and Table 21 (but with progression by INV not IRO assessment).

B6. Please provide EQ-5D scores for KEYNOTE-006 as displayed in Table 73 and Table 75 of the company submission for the 10 mg/kg Q2W separately and then combined with the other two pembrolizumab arms. Please clarify why utility values for the patients in the 10 mg/Q2W arm of the trial were not pooled in the initial analysis.

Section C: Textual clarifications and additional points

None

ERG responses to company queries re clarification requests.

24th June 2015

Company query	ERG response
Question B1. All patients who were randomised to the ipilimumab treatment arm received the first dose of ipilimumab, as identified as part of the inputs in the model. We were unclear whether the question may be referring to something different than the first dose?	Approximately 20 patients who were randomised to ipilimumab withdrew before the start of the trial. These are shown as censored in the KM charts. It appears in the model that these are excluded from any PFS or OS curves and as such the analysis would appear to be per protocol rather than ITT as stated. Please can you clarify?
Question B3. Can you please clarify further what is meant by the three subgroups 'pembrolizumab treated (both regimens)', 'ipilimumab treated' and 'ipilimumab untreated'? With 'pembrolizumab treated (both regimens)', is the ERG referring to patients treated in either the 10mg/kg Q3W and the 10mg/kg Q2W treatment groups, or to some specific subgroups of patients within these treatment arms? What is the difference between 'ipilimumab treated' and 'ipilimumab untreated'? Given that in the ipilimumab treatment arm not all patients received the second, third and fourth doses, how would the ERG like this to be addressed when presenting the table with the baseline characteristics?	'Pembrolizumab treated (both regimens)' refers to both the Q3W and Q2W groups, i.e. for the purposes of this question all patients who receive pembrolizumab may be considered as one group 'Ipilimumab untreated' refers to patients who withdrew before the trial started (i.e. the 20 patients highlighted in question B1) Please provide baseline characteristics as requested (stratification by number of treatments is not necessary)
Question B6. Can the ERG please clarify what it is meant by providing EQ-5D scores 'for the 10mg/kg Q2W separately and then combined with the other two pembrolizumab arms'? Do they perhaps mean pooling both pembrolizumab treatment arms (10mg/kg Q3W and Q2W) with the ipilimumab treatment arm?	Apologies for the confusion. We would like two separate analyses, i.e. EQ-5D scores generated for: 1. the Q2W arm 2. the Q2W arm, the Q3W arm and the ipilimumab arm (pooled)

- The ERG has an additional clarification request regarding the company's network meta-analysis.

<u>Additional question:</u>

With reference to Table 41 of the CS:

NMAs were performed for four scenario networks to provide results for the outcomes of PFS and OS. OS results were generated only for scenario 3a. The ERG assumes that this is because Hersh et al do not provide PFS curves; however, for scenario 1, PFS data for Hersh et al were generated using the OS data and the relationship between HR PFS and HR OS based on a method described by Flaherty et al. (2014). The ERG would like to request

clarification as to why the Flaherty method was not used to provide PFS results for Hersh et al for scenario 3a.

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3rd July 2015

Dear Janet,

Re. Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

MSD welcomes the opportunity to answer the clarification questions and our responses are provided below.

Should NICE or the ERG require any further clarification we would be more than happy to provide an answer to them.

Kind regards,

[redacted], [redacted]

Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

Dear [redacted],

The Evidence Review Group (ERG), Liverpool Reviews & Implementation Group (LRiG), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 29 May 2015 by Merck Sharp & Dohme. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some aspects of the clinical and cost effectiveness data.

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We request you to provide a written response to this letter to the Institute by **5pm** on **3 July 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:

If you have any queries related to this letter, please contact [redacted], Project Manager [redacted] in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Clinical-effectiveness data:

A1. **If available, please provide a copy of the European Medicine Agency (EMA) EPAR for pembrolizumab. If the EPAR is not available, please provide a detailed rationale for the use of the 2mg/kg dose (licensed dose) rather than the 10mg/kg dose (KEYNOTE-006) for the patient population considered in this appraisal.**

At the moment MSD only has a copy of the CHMP assessment report from which the EPAR is derived. The following has been taken from the CHMP assessment report (attached to this response) and provides the rationale for the use of the 2mg/kg dose:

"Alternative schedules (10 mg/kg Q3w and 10 mg/kg Q2W) were evaluated in Study P001, and also in the ongoing comparative studies P002 (IPI-refractory patients: 2mg/kg Q3W or 10 mg/kg Q3W) and P006 (IPInaive patients: 10 mg/kg Q3W or 10 mg/kg Q2W). The CHMP was initially concerned that the 10 mg/kg dose in study P002 had shown a better efficacy compared with the proposed dose 2 mg/kg for the indication. A higher ORR at 10 mg/kg Q2W dose was shown in comparison to other doses tested (2 mg/kg Q3W, 10 mg/kg Q3W) in cohort B1 as well. Subsequent investigations and analyses across studies presented by the applicant demonstrated that this high response in a single group appeared to be a chance event as the totality of the currently available data, including randomized cohort comparisons, was consistent with a lack of statistically significant and clinically meaningful differences in response across these doses and regimens. Exposure-response analyses at the individual trial level revealed that no clinically relevant exposure-response relationship was observed. Further analyses with an integrated exposure-response analysis for clinical efficacy, including all melanoma studies (P001, P002 and P006) showed a non- significant relationship between pembrolizumab exposure and change in tumour size, which was slightly more evident in IPI-naïve patients. Box plots representing the 25th-75th percentile spread of change in tumour showed an overlap between the boxes at the different exposure level, with no apparent exposure-response relationship. No differences were seen across the wide range of exposures (<660 µg/ml to >8010 µg/ml) and doses (1 to 10 mg/kg). Based on these analyses, the CHMP is reassured that the extrapolation of the data shown in the trial P006 with the dose 10 mg/kg can be considered applicable for the 2mg/kg and that no differences in the efficacy are to be expected between the two doses." (page126).

Statistical methods:

A2. Regarding the final analysis of KEYNOTE-006, it is stated on page 65 of the company submission:

"Since patients in the ipilimumab arm were expected to discontinue treatment earlier compared to patients in the pembrolizumab arms, and patients who discontinued ipilimumab were likely to receive other PD-1 treatments similar to pembrolizumab after discontinuation….The 95% confidence intervals for the HR for OS before or after proper adjustment of the cross-over effect will be provided at the final analysis (therefore not of relevance to IA1 and IA2 results)".

However, it is then stated on page 87 of the company submission:

"As OS was positive at IA2, no formal OS analysis will be conducted at the planned final analysis. However, patients will continue to be followed up and long-term survival for this study will be updated as deemed appropriate."

a. Please clarify why this final analysis will not be performed; without this analysis, the impact of crossover to other treatments appears to not have been properly adjusted for in the results presented for IA1 and IA2.

The use of other PD-1 treatments after discontinuation of ipilimumab is likely to underestimate the true survival benefit of pembrolizumab over ipilimumab (since it bias HR towards the null). Despite that, at the second interim analysis (IA2) pembrolizumab has shown a significant improvement in OS (HR = 0.69; p=0.00358) when directly compared with ipilimumab. Based on this, the study's independent Data Monitoring Committee (DMC) considered that KEYNOTE-006 had met its primary endpoints, recommended to stop the study early and considered the IA2 as the definitive OS analysis. Patients continued to be followed up and MSD agrees that, although the final OS analysis won't change the conclusions on the positive survival effect of pembrolizumab, it will provide important insight into how the cross-over to other treatments may have underestimated the overall survival findings. So, exploratory analysis adjusting for subsequent anti-cancer therapy will be provided at the final analysis of OS, expected to be completed in the second half of 2016. The exact time for this analysis is not yet known, since it is event driven.

b. Please provide a list of other treatments received by patients in the KEYNOTE-006 trial following discontinuation.

Exploratory analysis of OS adjusting for subsequent anti-cancer therapy was not performed at IA1 and IA2. At IA2, OS is statistically significant in both pembrolizumab arms at the pre-specified alpha level of 0.005 using the Hochberg step-up procedure without adjusting for non-study treatment (also see response above). A table summarizing new anti-cancer therapy after patients discontinued study treatment is provided below (Table 1). A slight

higher number of ipilimumab patients started on new anti-cancer therapy compared to pembrolizumab patients.

Table 1: Summary of New Oncologic Therapies after Discontinuing from Study Treatment (ITT Population)

	Ipilimumab 3 mg/kg		Pembrolizumab 10 mg/kg Q2W		Pembrolizumab 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	278	(100.0)	279	(100.0)	277	(100.0)	834	(100.0)
With one or more new Systemic Therapies	92	(33.1)	72	(25.8)	79	(28.5)	243	(29.1)
BRAF Inhibitor	36	(12.9)	26	(9.3)	21	(7.6)	83	(10.0)
BRAF Inhibitor + Other	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.1)
BRAF+MEK Inhibitor	5	(1.8)	1	(0.4)	1	(0.4)	7	(0.8)
Chemotherapy	25	(9.0)	11	(3.9)	17	(6.1)	53	(6.4)
Chemotherapy + Other	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
Immunotherapy	35	(12.6)	36	(12.9)	42	(15.2)	113	(13.5)
Immunotherapy + Chemotherapy	1	(0.4)	1	(0.4)	0	(0.0)	2	(0.2)
MEK Inhibitor	17	(6.1)	13	(4.7)	7	(2.5)	37	(4.4)
Other	7	(2.5)	0	(0.0)	1	(0.4)	8	(1.0)
Summary of new Oncologic Therapies								
BRAF Inhibitor	**36**	**(12.9)**	**26**	**(9.3)**	**21**	**(7.6)**	**83**	**(10.0)**
Dabrafenib	20	(7.2)	18	(6.5)	14	(5.1)	52	(6.2)
Encorafenib	2	(0.7)	0	(0.0)	0	(0.0)	2	(0.2)
Raf Kinase B Inhibitor (Unspecified)	0	(0.0)	2	(0.7)	0	(0.0)	2	(0.2)
Vemurafenib	17	(6.1)	9	(3.2)	11	(4.0)	37	(4.4)
BRAF Inhibitor + Other	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.1)**
Cyclin Dependent Kinase Inhibitor (Unspecified) (+) Vemurafenib	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.1)
BRAF+MEK Inhibitor†	**5**	**(1.8)**	**1**	**(0.4)**	**1**	**(0.4)**	**7**	**(0.8)**
Dabrafenib (+) Trametinib	4	(1.4)	1	(0.4)	1	(0.4)	6	(0.7)
Trametinib (+) Vemurafenib	2	(0.7)	0	(0.0)	0	(0.0)	2	(0.2)
Chemotherapy	**25**	**(9.0)**	**11**	**(3.9)**	**17**	**(6.1)**	**53**	**(6.4)**
Carboplatin	3	(1.1)	1	(0.4)	0	(0.0)	4	(0.5)
Carboplatin (+) Dacarbazine	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
Carboplatin (+) Paclitaxel	2	(0.7)	1	(0.4)	1	(0.4)	4	(0.5)
Cisplatin (+) Dacarbazine	2	(0.7)	0	(0.0)	1	(0.4)	3	(0.4)
Dacarbazine	12	(4.3)	4	(1.4)	7	(2.5)	23	(2.8)
Docetaxel	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
Evofosfamide	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
Fotemustine	1	(0.4)	3	(1.1)	1	(0.4)	5	(0.6)
Paclitaxel	5	(1.8)	2	(0.7)	1	(0.4)	8	(1.0)
Temozolomide	8	(2.9)	2	(0.7)	3	(1.1)	13	(1.6)
Chemotherapy + Other	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.4)**	**1**	**(0.1)**
Paclitaxel (+) Pazopanib Hydrochloride	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
Immunotherapy	**35**	**(12.6)**	**36**	**(12.9)**	**42**	**(15.2)**	**113**	**(13.5)**
Anti-Pdl1 Monoclonal Antibody (Unspecified)	3	(1.1)	0	(0.0)	0	(0.0)	3	(0.4)
Interleukin 2	3	(1.1)	0	(0.0)	1	(0.4)	4	(0.5)
Ipilimumab	9	(3.2)	33	(11.8)	41	(14.8)	83	(10.0)
Nivolumab	14	(5.0)	0	(0.0)	0	(0.0)	14	(1.7)
Other	6	(2.2)	3	(1.1)	1	(0.4)	10	(1.2)
Immunotherapy + Chemotherapy	**1**	**(0.4)**	**1**	**(0.4)**	**0**	**(0.0)**	**2**	**(0.2)**
Fotemustine (+) Ipilimumab	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.1)

Interleukin 2 (+) Cyclophosphamide (+) Fludarabine Phosphate (+) Tils	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
MEK inhibitor	**17 (6.1)**	**13 (4.7)**	**7 (2.5)**	**37 (4.4)**
Binimetinib	2 (0.7)	0 (0.0)	1 (0.4)	3 (0.4)
Trametinib	15 (5.4)	11 (3.9)	5 (1.8)	31 (3.7)
Unspecified	0 (0.0)	2 (0.7)	1 (0.4)	3 (0.4)
Other	**7 (2.5)**	**0 (0.0)**	**1 (0.4)**	**8 (1.0)**
Aflibercept	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.2)
Antineoplastic (Unspecified)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Cyclin Dependent Kinase Inhibitor (Unspecified)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Imatinib Mesylate	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Multi-Targeted Kinase Inhibitor (Unspecified)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Nilotinib	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.2)
Pi3 Kinase Inhibitor (Unspecified)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)

† BRAF+MEK Inhibitor: includes BRAF inhibitors or MEK inhibitors
Every patient is counted a single time for each applicable row and column
(Database Cut-off Date: 03SEP2014).

A3. **Tables 22, 24, 26, 27, and 29 of the company submission present two-sided p-values based on the log-rank test for comparisons between pembrolizumab 10 mg/kg Q2W and pembrolizumab 10 mg/kg Q3W. Please clarify whether this two-sided hypothesis testing was pre-specified for KEYNOTE-006.**

The analyses comparing the two regimens of pembrolizumab (10mg/Kg Q2W vs. 10mg/Kg Q3W) were not pre-specified in the protocol of KEYNOTE-006.

A4. **Please clarify how the range was obtained for response duration in Table 31 of the company submission. It is unclear as the median has not been reached but the range is given.**

Table 31 in page 90 of MSD original submission [ID801] is provided again below as Table 2. The range of values presented are for the duration of responses observed, and not the range of the median, which was not reached. MSD agrees that the way the results are presented can lead to misinterpretation and updated the table for purposes of clarity.

Table 2: KEYNOTE-006 - Summary of Time to Response and Response Duration for Subjects with Objective Response (ITT Population)

	Ipilimumab 3 mg/kg	Pembrolizumab 10 mg/kg Q3W	Pembrolizumab 10 mg/kg Q2W	Pembrolizumab combined
	(N=278)	(N=277)	(N=279)	(N=556)
IRO Assessment per RECIST 1.1				
Number of Patients with Response†	33	91	94	185
Time to Response † (days)				

• Mean (SD) • Median (Range)	106 (36) 87 (80-250)	99 (35) 85 (36-251)	95 (26) 86 (32-212)	97 (31) 85 (32-251)
Response Duration‡ (days) • Median (Range of response durations)§	Not reached (33+ - 239+)	Not reached (42+ - 246+)	251 (42+ - 251)	251 (42+ - 251)
Number of Response Ongoing (%)	29 (88)	88 (97)	84 (89)	172 (93)
Investigator Assessment per irRC				
Number of Patients with Response†	45	104	104	208
Time to Response † (days) • Mean (SD) • Median (Range)	108 (36) 87 (43-202)	95 (25) 85 (58-212)	98 (30) 86 (58-216)	97 (28) 85 (58-216)
Response Duration‡ (days)				
• Median (Range of response durations)§	Not reached (33+ - 254+)	Not reached (42+ - 253+)	Not reached (29+ - 254+)	Not reached (29+ - 254+)
Number of Response Ongoing (%)	41 (91)	96 (92)	97 (93)	193 (93)

Independent Radiologist plus Oncologist Review.
IRC: Independent Review Committee.
† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
‡ From product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates there is no progressive disease by the time of last disease assessment.
(Database cut-off date: 03SEP2014)

A5. **For the sample size calculation for KEYNOTE-006 described on page 63 of the company submission, please provide the parameters used for the exponential distribution. Please also confirm that the power to demonstrate superiority used for the sample size calculation is 85%.**

The assumptions made for the sample size estimation for KEYNOTE-006 were described on page 63 of our submission. The sample size calculation was driven by survival events. Overall survival was assumed to follow an exponential distribution with a median of 10-11 months in ipilimumab arm (both 10 and 11 months were looked at as OS median in the control arm). With approximately 300 OS events between one pembrolizumab arm and the ipilimumab arm, the study has 85% power to demonstrate superiority in OS at type I error rate of 2.0% (one-sided) when the true hazard ratio for OS is 0.70. Since the Hochberg step-up procedure is used to test OS superiority, the overall study power for OS under various hazard ratios is demonstrated in

Table 3 below.

Table 3: Overall Study Power for OS under Various Hazard Ratios using Hochberg Procedure

True HR (Pembrolizumab Q2W/ Ipilimumab 3 mg/kg)	True HR (Pembrolizumab Q3W/ Ipilimumab 3 mg/kg)	Pr (positive for Pembrolizumab Q2W arm)*	Pr (positive for Pembrolizumab Q3W arm)*	Pr (positive for at least one arm of Pembrolizumab)
0.6	0.6	0.99	0.99	>0.99
0.6	0.65	0.99	0.95	0.99
0.6	0.7	0.99	0.85	0.99
0.65	0.65	0.95	0.95	0.98
0.65	0.7	0.94	0.84	0.96
0.65	0.75	0.93	0.67	0.94
0.7	0.7	0.83	0.83	0.91
0.7	0.75	0.81	0.65	0.85
0.7	0.8	0.80	0.44	0.81

*Assumptions: 1) 300 OS events between each pembrolizumab arm and control, Hochberg procedure is used at 2.0% type I error rate; 2) Correlation between two treatment effects (Q3W vs. control and Q2W vs. control) is 0.5

A6. Page 167 of the company submission states that the Schoenfeld residual test was used to test the assumption of proportional hazards.

a. Please confirm whether the proportional hazards assumption for progression-free survival was assessed for the complete trial period or only for the first 12 weeks.

For PFS, the proportional hazards assumption was assessed from week 13 onwards (until the cut-off date of Interim Analysis 1), which reflected a median follow-up time of 7.9 months (with the maximum follow-up being 63 weeks). The reason to consider the analysis from week 13 was the protocol-driven drop in PFS experienced by patients at week 12-13 (see section 5.3.3., page 165 of the submission). Up to week 12 the model used PFS KM curves.

b. Please confirm whether the Schoenfeld residuals method was also used for testing proportional hazards for the primary analysis of overall survival.

The Schoenfeld residuals method was also used to test for proportional hazards for the primary analysis of overall survival (see page 170 of the submission). The cumulative hazard plot was presented in Figure 27.

c. Please confirm whether the Schoenfeld residuals method was pre-specified for the testing of the proportional hazards assumption.

The KEYNOTE-006 protocol did not pre-specify any test to assess the assumption of proportional hazards. The Schoenfeld test was used since this allowed us to present log-cumulative hazard plots and residual plots as recommended by the DSU for survival analyses for economic evaluations alongside clinical trials (Latimer 2011).

d. Please clarify what is meant by the 'non-parametric Kaplan-Meier method' which is specified in the clinical study report to be used for the analysis of progression-free survival.

The Kaplan-Meier method is used to estimate the PFS curve in each treatment group. The Kaplan-Meier method is a non-parametric method, allowing the analysis of data without assuming an underlying distribution.

A7. **Please provide justification for why one-sided hypothesis testing has been used for KEYNOTE-006. It is common practice for phase III trials to use two-sided hypothesis testing. Please also justify why the sample size calculation was carried out using a one-sided p-value as the sample size is likely to be smaller as a result of using a one-sided hypothesis test.**

KEYNOTE-006 was a phase III trial designed to test the hypothesis that at least one pembrolizumab arm is superior to ipilimumab in PFS at an interim analysis or at least one pembrolizumab arm is superior to ipilimumab in OS at either an interim analysis or the final analysis of OS. Both the hypothesis testing for superiority and the correspondent sample size estimation were based on one-side p-values.

The one-sided hypothesis testing is pre-specified in the protocol, which is usually preferred in a superiority trial. A one-sided alpha=0.025 is equivalent to a two-sided alpha =0.05 in terms of statistical significance in superiority testing.

A8. **Please provide the p-values for the tests for interaction for the subgroup analyses presented in Figures 14–17 of the company submission.**

Please find below the requested p-values for the tests for interaction for the subgroup analyses presented in Figures 14-17 of the submission document. The p-values are available in the various tables (Table 4 to Table 24) for each of the treatment comparisons.

For the subgroup analyses, interaction term of treatment group and subgroup is not included in the model. The hazard ratio and its 95% CI are estimated using a stratified Cox model with treatment and subgroup as covariates and stratified by the stratification factors used for randomisation (line of therapy, ECOG at baseline, PD-L1 expression status).

Table 4: Analysis of Progression-Free Survival Based on IRO Assessment (Primary Censoring Rule); RECIST v1.1 by Gender (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
Male									
Ipilimumab 3 mg/kg	162	99 (61.1)	552.2	17.9	2.9 (2.8, 4.0)	33.7 (25.7, 41.9)	---	---	---
Pembrolizumab 10 mg/kg Q2W	161	77 (47.8)	821.7	9.4	8.2 (4.7, 12.7)	56.0 (47.8, 63.4)	0.55 (0.40, 0.74)	0.0001	<.0001
Pembrolizumab 10 mg/kg Q3W	174	88 (50.6)	882.3	10.0	8.2 (3.7, 11.9)	53.5 (45.7, 60.7)	0.57 (0.42, 0.77)	0.0002	0.0002
Female									
Ipilimumab 3 mg/kg	116	89 (76.7)	358.6	24.8	2.8 (2.8, 2.9)	17.2 (10.4, 25.4)	---	---	---
Pembrolizumab 10 mg/kg Q2W	118	80 (67.8)	512.8	15.6	2.9 (2.8, 5.3)	35.8 (27.0, 44.7)	0.62 (0.45, 0.85)	0.0026	0.0021
Pembrolizumab 10 mg/kg Q3W	103	69 (67.0)	420.8	16.4	2.9 (2.8, 4.1)	34.2 (24.9, 43.7)	0.59 (0.43, 0.83)	0.0022	0.0017
Treatment-by-subgroup interaction							p-Value based on Q-statistic	I^2 statistic (%)	
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg							0.5843	0.00	
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg							0.8443	0.00	

[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)
[§] Two-sided p-value based on Wald-test
[‖] Two-sided p-value based on log-rank test
(Database Cutoff Date: 03SEP2014)

Table 5: Analysis of Progression-Free Survival Based on IRO Assessment (Primary Censoring Rule); RECIST v1.1 by Age Category (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
<65									
Ipilimumab 3 mg/kg	166	113 (68.1)	508.0	22.2	2.8 (2.8, 2.9)	22.7 (15.8, 30.4)	---	---	---
Pembrolizumab 10 mg/kg Q2W	153	89 (58.2)	723.6	12.3	4.2 (3.0, 7.4)	44.1 (35.9, 52.1)	0.55 (0.41, 0.73)	<.0001	<.0001
Pembrolizumab 10 mg/kg Q3W	152	90 (59.2)	695.8	12.9	3.4 (2.9, 5.8)	42.0 (33.9, 49.9)	0.59 (0.45, 0.79)	0.0003	0.0003
>=65									
Ipilimumab 3 mg/kg	112	75 (67.0)	402.8	18.6	2.8 (2.8, 3.8)	31.5 (22.6, 40.8)	---	---	---
Pembrolizumab 10 mg/kg Q2W	126	68 (54.0)	610.8	11.1	6.2 (2.9, 11.6)	51.1 (41.8, 59.6)	0.61 (0.43, 0.86)	0.0045	0.0039
Pembrolizumab 10 mg/kg Q3W	125	67 (53.6)	607.3	11.0	6.9 (2.9, 9.7)	51.9 (42.6, 60.4)	0.57 (0.41, 0.81)	0.0015	0.0013
Treatment-by-subgroup interaction							p-Value based on Q-statistic	I^2 statistic (%)	
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg							0.6525	0.00	
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg							0.8824	0.00	

[†] From product-limit (Kaplan-Meier) method for censored data

[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)

[§] Two-sided p-value based on Wald-test

[‖] Two-sided p-value based on log-rank test

(Database Cutoff Date: 03SEP2014)

Table 6: Analysis of Progression-Free Survival Based on IRO Assessment (Primary Censoring Rule); RECIST v1.1 by Country: United States vs Rest of The World (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
United States									
Ipilimumab 3 mg/kg	64	32 (50.0)	176.6	18.1	2.9 (2.8, 5.5)	32.9 (19.6, 46.8)	---	---	---
Pembrolizumab 10 mg/kg Q2W	50	21 (42.0)	233.6	9.0	11.0 (2.8, 11.6)	58.5 (42.9, 71.2)	0.46 (0.26, 0.83)	0.0102	0.0079
Pembrolizumab 10 mg/kg Q3W	47	20 (42.6)	238.4	8.4	8.2 (2.8, .)	64.4 (48.7, 76.5)	0.43 (0.23, 0.79)	0.0065	0.0054
Other									
Ipilimumab 3 mg/kg	214	156 (72.9)	734.3	21.2	2.8 (2.8, 2.9)	25.4 (19.4, 31.9)	---	---	---
Pembrolizumab 10 mg/kg Q2W	229	136 (59.4)	1100.9	12.4	4.7 (3.2, 6.2)	45.1 (38.4, 51.6)	0.59 (0.47, 0.75)	<.0001	<.0001
Pembrolizumab 10 mg/kg Q3W	230	137 (59.6)	1064.7	12.9	3.7 (2.9, 4.9)	42.8 (36.2, 49.2)	0.60 (0.48, 0.76)	<.0001	<.0001

Treatment-by-subgroup interaction	p-Value based on Q-statistic	I^2 statistic (%)
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg	0.4459	0.00
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg	0.3062	4.48

[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)
[§] Two-sided p-value based on Wald-test
[‖] Two-sided p-value based on log-rank test
(Database Cutoff Date: 03SEP2014)

Table 7: Analysis of Progression-Free Survival Based on IRO Assessment (Primary Censoring Rule); RECIST v1.1 by ECOG performance status at Screening (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
0									
Ipilimumab 3 mg/kg	188	121 (64.4)	640.4	18.9	2.9 (2.8, 3.3)	30.4 (23.4, 37.8)	---	---	---
Pembrolizumab 10 mg/kg Q2W	196	103 (52.6)	981.6	10.5	6.1 (4.2, 8.8)	50.6 (43.2, 57.6)	0.55 (0.42, 0.72)	<.0001	<.0001
Pembrolizumab 10 mg/kg Q3W	189	108 (57.1)	925.1	11.7	4.1 (3.1, 7.8)	46.4 (39.0, 53.4)	0.62 (0.48, 0.81)	0.0004	0.0004
1									
Ipilimumab 3 mg/kg	90	67 (74.4)	270.5	24.8	2.6 (1.9, 2.8)	19.5 (11.4, 29.3)	---	---	---
Pembrolizumab 10 mg/kg Q2W	83	54 (65.1)	352.9	15.3	2.9 (2.7, 6.2)	39.6 (28.8, 50.2)	0.63 (0.43, 0.93)	0.0184	0.0170
Pembrolizumab 10 mg/kg Q3W	88	49 (55.7)	378.0	13.0	3.1 (2.8, 10.4)	46.8 (35.9, 57.0)	0.53 (0.36, 0.78)	0.0011	0.0009
Treatment-by-subgroup interaction							p-Value based on Q-statistic	I^2 statistic (%)	
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg							0.5464	0.00	
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg							0.4975	0.00	

[†] From product-limit (Kaplan-Meier) method for censored data

[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)

[§] Two-sided p-value based on Wald-test

[‖] Two-sided p-value based on log-rank test

(Database Cutoff Date: 03SEP2014)

Table 8: Analysis of Progression-Free Survival Based on IRO Assessment (Primary Censoring Rule); RECIST v1.1by PDL1 Status at Baseline (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
PD-L1 Negative									
Ipilimumab 3 mg/kg	47	33 (70.2)	145.7	22.6	2.8 (2.6, 3.0)	27.2 (14.5, 41.4)	---	---	---
Pembrolizumab 10 mg/kg Q2W	49	33 (67.3)	225.0	14.7	4.3 (2.8, 6.1)	38.7 (24.9, 52.3)	0.67 (0.41, 1.11)	0.1198	0.1121
Pembrolizumab 10 mg/kg Q3W	54	41 (75.9)	218.0	18.8	2.8 (2.7, 3.0)	28.3 (17.0, 40.7)	0.76 (0.47, 1.24)	0.2751	0.2729
PD-L1 Positive									
Ipilimumab 3 mg/kg	225	153 (68.0)	741.6	20.6	2.8 (2.8, 3.0)	25.6 (19.5, 32.1)	---	---	---
Pembrolizumab 10 mg/kg Q2W	225	119 (52.9)	1094.7	10.9	6.2 (3.7, 9.2)	50.5 (43.6, 57.0)	0.53 (0.41, 0.67)	<.0001	<.0001
Pembrolizumab 10 mg/kg Q3W	221	115 (52.0)	1079.6	10.7	6.4 (4.0, 14.6)	51.0 (44.1, 57.5)	0.52 (0.40, 0.66)	<.0001	<.0001
Treatment-by-subgroup interaction							p-Value based on Q-statistic	I^2 statistic (%)	
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg							0.4025	0.00	
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg							0.1630	48.61	

[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)
[§] Two-sided p-value based on Wald-test
[‖] Two-sided p-value based on log-rank test
(Database Cutoff Date: 03SEP2014)

Table 9: Analysis of Progression-Free Survival Based on IRO Assessment (Primary Censoring Rule); RECIST v1.1by BRAF status (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
Wild-type									
Ipilimumab 3 mg/kg	170	111 (65.3)	566.9	19.6	2.8 (2.8, 3.0)	28.6 (21.3, 36.4)	---	---	---
Pembrolizumab 10 mg/kg Q2W	177	102 (57.6)	875.5	11.7	5.6 (3.2, 8.2)	47.2 (39.5, 54.5)	0.58 (0.44, 0.76)	0.0001	<.0001
Pembrolizumab 10 mg/kg Q3W	178	97 (54.5)	870.9	11.1	4.8 (2.9, 9.1)	49.0 (41.2, 56.2)	0.57 (0.43, 0.75)	<.0001	<.0001
Mutant, anti-BRAF									
Ipilimumab 3 mg/kg	52	38 (73.1)	141.4	26.9	2.8 (2.1, 3.2)	11.6 (4.0, 23.4)	---	---	---
Pembrolizumab 10 mg/kg Q2W	43	27 (62.8)	188.1	14.4	3.4 (2.7, 7.4)	43.8 (28.7, 57.9)	0.58 (0.34, 0.97)	0.0383	0.0341
Pembrolizumab 10 mg/kg Q3W	44	33 (75.0)	153.9	21.4	2.8 (2.6, 2.9)	25.0 (13.5, 38.4)	0.87 (0.53, 1.40)	0.5604	0.5601
Mutant, no anti-BRAF									
Ipilimumab 3 mg/kg	55	39 (70.9)	192.9	20.2	2.9 (2.7, 4.3)	31.9 (19.2, 45.3)	---	---	---
Pembrolizumab 10 mg/kg Q2W	55	25 (45.5)	255.2	9.8	7.0 (2.9, .)	52.6 (37.7, 65.5)	0.54 (0.32, 0.91)	0.0218	0.0192
Pembrolizumab 10 mg/kg Q3W	53	26 (49.1)	264.9	9.8	9.7 (3.1, .)	54.3 (39.6, 66.8)	0.44 (0.26, 0.75)	0.0023	0.0018
Treatment-by-subgroup interaction							p-Value based on Q-statistic	I^2 statistic (%)	
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg							0.9688	0.00	
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg							0.1573	45.94	

[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)
[§] Two-sided p-value based on Wald-test
[‖] Two-sided p-value based on log-rank test
(Database Cutoff Date: 03SEP2014)

Table 10: Analysis of Progression-Free Survival Based on IRO Assessment (Primary Censoring Rule); RECIST v1.1by Line of Systemic Therapy (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
First Line									
Ipilimumab 3 mg/kg	181	123 (68.0)	609.5	20.2	2.8 (2.8, 3.0)	28.6 (21.5, 35.9)	---	---	---
Pembrolizumab 10 mg/kg Q2W	183	97 (53.0)	889.8	10.9	5.6 (4.0, 12.2)	49.3 (41.6, 56.5)	0.55 (0.42, 0.72)	<.0001	<.0001
Pembrolizumab 10 mg/kg Q3W	185	94 (50.8)	919.6	10.2	6.9 (4.0, 9.8)	53.2 (45.5, 60.3)	0.50 (0.38, 0.66)	<.0001	<.0001
Second Line									
Ipilimumab 3 mg/kg	97	65 (67.0)	301.3	21.6	2.9 (2.8, 3.2)	22.5 (13.8, 32.5)	---	---	---
Pembrolizumab 10 mg/kg Q2W	96	60 (62.5)	444.7	13.5	3.2 (2.8, 6.4)	43.6 (33.3, 53.4)	0.63 (0.44, 0.90)	0.0121	0.0105
Pembrolizumab 10 mg/kg Q3W	91	63 (69.2)	376.8	16.7	2.8 (2.8, 3.4)	32.5 (23.1, 42.2)	0.80 (0.56, 1.14)	0.2103	0.2061
Treatment-by-subgroup interaction							p-Value based on Q-statistic	I^2 statistic (%)	
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg							0.5589	0.00	
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg							0.0427	75.64	

[†] From product-limit (Kaplan-Meier) method for censored data

[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)

[§] Two-sided p-value based on Wald-test

[‖] Two-sided p-value based on log-rank test

(Database Cutoff Date: 03SEP2014)

Table 11: Analysis of Overall Survival by Gender (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 6 in %† (95% CI)	Treatment vs. Control		
							Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
Male									
Ipilimumab 3 mg/kg	162	61 (37.7)	1449.3	4.2	Not Reached (11.9, .)	74.4 (66.5, 80.8)	---	---	---
Pembrolizumab 10 mg/kg Q2W	161	44 (27.3)	1867.1	2.4	Not Reached (15.9, .)	86.2 (79.8, 90.7)	0.57 (0.39, 0.84)	0.0050	0.0045
Pembrolizumab 10 mg/kg Q3W	174	56 (32.2)	1971.2	2.8	Not Reached (., .)	87.3 (81.3, 91.4)	0.66 (0.45, 0.95)	0.0246	0.0236
Female									
Ipilimumab 3 mg/kg	116	51 (44.0)	1123.0	4.5	15.4 (11.6, .)	74.6 (65.4, 81.7)	---	---	---
Pembrolizumab 10 mg/kg Q2W	118	41 (34.7)	1285.7	3.2	Not Reached (14.7, .)	82.8 (74.6, 88.5)	0.69 (0.46, 1.04)	0.0788	0.0780
Pembrolizumab 10 mg/kg Q3W	103	36 (35.0)	1134.6	3.2	Not Reached (., .)	87.2 (79.0, 92.4)	0.78 (0.51, 1.21)	0.2689	0.2705
Treatment-by-subgroup interaction							p-Value based on Q-statistic	I^2 statistic (%)	
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg							0.5169	0.00	
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg							0.5436	0.00	

† From product-limit (Kaplan-Meier) method for censored data

‡ Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)

§ Two-sided p-value based on Wald-test

‖ Two-sided p-value based on log-rank test

(Database Cutoff Date: 03MAR2015)

Table 12: Analysis of Overall Survival by Age Category (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
<65									
Ipilimumab 3 mg/kg	166	61 (36.7)	1543.4	4.0	Not Reached (13.9, .)	77.9 (70.4, 83.8)	---	---	---
Pembrolizumab 10 mg/kg Q2W	153	47 (30.7)	1752.4	2.7	Not Reached (., .)	86.8 (80.3, 91.3)	0.65 (0.44, 0.95)	0.0273	0.0261
Pembrolizumab 10 mg/kg Q3W	152	51 (33.6)	1717.6	3.0	Not Reached (., .)	88.7 (82.4, 92.8)	0.77 (0.53, 1.12)	0.1747	0.1733
>=65									
Ipilimumab 3 mg/kg	112	51 (45.5)	1028.9	5.0	14.0 (9.8, .)	69.7 (59.9, 77.5)	---	---	---
Pembrolizumab 10 mg/kg Q2W	126	38 (30.2)	1400.3	2.7	Not Reached (14.8, .)	82.3 (74.4, 88.0)	0.56 (0.36, 0.87)	0.0097	0.0090
Pembrolizumab 10 mg/kg Q3W	125	41 (32.8)	1388.1	3.0	Not Reached (., .)	85.5 (78.0, 90.6)	0.66 (0.44, 1.01)	0.0551	0.0543

Treatment-by-subgroup interaction	p-Value based on Q-statistic	I^2 statistic (%)
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg	0.6328	0.00
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg	0.5988	0.00

[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)
[§] Two-sided p-value based on Wald-test
[‖] Two-sided p-value based on log-rank test
(Database Cutoff Date: 03MAR2015)

Table 13: Analysis of Overall Survival by Country: United States vs Rest of The World (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
United States									
Ipilimumab 3 mg/kg	64	13 (20.3)	582.1	2.2	Not Reached (., .)	87.0 (74.6, 93.6)	---	---	---
Pembrolizumab 10 mg/kg Q2W	50	7 (14.0)	585.5	1.2	Not Reached (., .)	93.7 (81.7, 97.9)	0.49 (0.19, 1.26)	0.1364	0.1302
Pembrolizumab 10 mg/kg Q3W	47	8 (17.0)	555.8	1.4	Not Reached (., .)	89.4 (76.3, 95.4)	0.55 (0.22, 1.39)	0.2061	0.1998
Other									
Ipilimumab 3 mg/kg	214	99 (46.3)	1990.2	5.0	14.0 (10.9, .)	71.3 (64.5, 77.0)	---	---	---
Pembrolizumab 10 mg/kg Q2W	229	78 (34.1)	2567.3	3.0	Not Reached (15.9, .)	82.9 (77.4, 87.2)	0.62 (0.46, 0.84)	0.0019	0.0017
Pembrolizumab 10 mg/kg Q3W	230	84 (36.5)	2549.9	3.3	Not Reached (., .)	86.8 (81.7, 90.6)	0.65 (0.49, 0.88)	0.0045	0.0042

Treatment-by-subgroup interaction	p-Value based on Q-statistic	I^2 statistic (%)
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg	0.6261	0.00
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg	0.7230	0.00

[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)
[§] Two-sided p-value based on Wald-test
[‖] Two-sided p-value based on log-rank test
(Database Cutoff Date: 03MAR2015)

Table 14: Analysis of Overall Survival by ECOG performance status at Screening (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
0									
Ipilimumab 3 mg/kg	188	63 (33.5)	1840.9	3.4	Not Reached (15.4, .)	82.4 (75.8, 87.4)	---	---	---
Pembrolizumab 10 mg/kg Q2W	196	48 (24.5)	2365.5	2.0	Not Reached (., .)	91.8 (86.9, 94.9)	0.55 (0.37, 0.80)	0.0020	0.0017
Pembrolizumab 10 mg/kg Q3W	189	57 (30.2)	2212.7	2.6	Not Reached (., .)	92.6 (87.8, 95.5)	0.75 (0.52, 1.07)	0.1156	0.1141
1									
Ipilimumab 3 mg/kg	90	49 (54.4)	731.4	6.7	7.9 (5.8, .)	58.5 (47.2, 68.1)	---	---	---
Pembrolizumab 10 mg/kg Q2W	83	37 (44.6)	787.2	4.7	14.0 (12.2, .)	68.0 (56.7, 77.0)	0.71 (0.46, 1.09)	0.1190	0.1177
Pembrolizumab 10 mg/kg Q3W	88	35 (39.8)	893.1	3.9	Not Reached (12.7, .)	75.8 (65.3, 83.5)	0.60 (0.39, 0.94)	0.0243	0.0230

Treatment-by-subgroup interaction	p-Value based on Q-statistic	I^2 statistic (%)
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg	0.3903	0.00
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg	0.4577	0.00

[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)
[§] Two-sided p-value based on Wald-test
[‖] Two-sided p-value based on log-rank test
(Database Cutoff Date: 03MAR2015)

Table 15: Analysis of Overall Survival by PDL1 Status at Baseline (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
PD-L1 Negative									
Ipilimumab 3 mg/kg	47	21 (44.7)	440.5	4.8	14.2 (7.5, .)	72.7 (57.0, 83.5)	---	---	---
Pembrolizumab 10 mg/kg Q2W	49	22 (44.9)	492.4	4.5	14.0 (10.1, .)	79.2 (64.8, 88.2)	0.91 (0.49, 1.69)	0.7704	0.7707
Pembrolizumab 10 mg/kg Q3W	54	26 (48.1)	532.6	4.9	12.7 (9.5, .)	82.9 (69.6, 90.7)	1.02 (0.56, 1.85)	0.9594	0.9589
PD-L1 Positive									
Ipilimumab 3 mg/kg	225	90 (40.0)	2065.9	4.4	Not Reached (12.6, .)	74.2 (67.7, 79.7)	---	---	---
Pembrolizumab 10 mg/kg Q2W	225	61 (27.1)	2607.9	2.3	Not Reached (., .)	86.1 (80.8, 90.0)	0.55 (0.40, 0.76)	0.0003	0.0002
Pembrolizumab 10 mg/kg Q3W	221	64 (29.0)	2557.0	2.5	Not Reached (., .)	88.7 (83.7, 92.2)	0.58 (0.42, 0.79)	0.0008	0.0007

Treatment-by-subgroup interaction	p-Value based on Q-statistic	I^2 statistic (%)
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg	0.1496	51.83
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg	0.1015	62.72

[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)
[§] Two-sided p-value based on Wald-test
[‖] Two-sided p-value based on log-rank test
(Database Cutoff Date: 03MAR2015)

Table 16: Analysis of Overall Survival by BRAF Status (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 6 in %† (95% CI)	Treatment vs. Control		
							Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
Wild-type									
Ipilimumab 3 mg/kg	170	75 (44.1)	1534.4	4.9	14.2 (10.8, .)	73.2 (65.5, 79.4)	---	---	---
Pembrolizumab 10 mg/kg Q2W	177	57 (32.2)	1970.1	2.9	Not Reached (15.9, .)	84.0 (77.6, 88.6)	0.57 (0.40, 0.80)	0.0015	0.0013
Pembrolizumab 10 mg/kg Q3W	178	63 (35.4)	1976.2	3.2	Not Reached (., .)	87.5 (81.6, 91.6)	0.66 (0.47, 0.92)	0.0153	0.0145
Mutant, anti-BRAF									
Ipilimumab 3 mg/kg	52	24 (46.2)	433.4	5.5	11.9 (6.0, .)	66.7 (50.9, 78.4)	---	---	---
Pembrolizumab 10 mg/kg Q2W	43	18 (41.9)	463.0	3.9	Not Reached (11.6, .)	79.1 (63.6, 88.5)	0.67 (0.36, 1.25)	0.2116	0.2088
Pembrolizumab 10 mg/kg Q3W	44	19 (43.2)	450.4	4.2	Not Reached (9.5, .)	77.1 (61.6, 87.0)	0.84 (0.46, 1.54)	0.5712	0.5708
Mutant, no anti-BRAF									
Ipilimumab 3 mg/kg	55	13 (23.6)	588.6	2.2	Not Reached (., .)	84.6 (71.6, 92.0)	---	---	---
Pembrolizumab 10 mg/kg Q2W	55	9 (16.4)	676.4	1.3	Not Reached (14.9, .)	92.7 (81.6, 97.2)	0.71 (0.27, 1.88)	0.4965	0.4950
Pembrolizumab 10 mg/kg Q3W	53	9 (17.0)	658.9	1.4	Not Reached (., .)	94.3 (83.5, 98.1)	0.71 (0.30, 1.67)	0.4288	0.4267
Treatment-by-subgroup interaction							p-Value based on Q-statistic	I^2 statistic (%)	
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg							0.8361	0.00	
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg							0.7892	0.00	

† From product-limit (Kaplan-Meier) method for censored data
‡ Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)
§ Two-sided p-value based on Wald-test
‖ Two-sided p-value based on log-rank test
(Database Cutoff Date: 03MAR2015)

Table 17: Analysis of Overall Survival by Line of Systemic Therapy (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median[†] (Months) (95% CI)	Survival Rate at Month 6 in %[†] (95% CI)	Treatment vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]	p-Value[‖]
First Line									
Ipilimumab 3 mg/kg	181	71 (39.2)	1718.9	4.1	Not Reached (13.9, .)	76.4 (69.2, 82.1)	---	---	---
Pembrolizumab 10 mg/kg Q2W	183	50 (27.3)	2092.1	2.4	Not Reached (., .)	85.7 (79.7, 90.0)	0.58 (0.41, 0.84)	0.0039	0.0035
Pembrolizumab 10 mg/kg Q3W	185	56 (30.3)	2108.8	2.7	Not Reached (., .)	89.1 (83.6, 92.8)	0.68 (0.47, 0.96)	0.0294	0.0284
Second Line									
Ipilimumab 3 mg/kg	97	41 (42.3)	853.4	4.8	14.0 (10.9, .)	70.8 (59.9, 79.2)	---	---	---
Pembrolizumab 10 mg/kg Q2W	96	35 (36.5)	1060.7	3.3	Not Reached (13.7, .)	83.1 (73.9, 89.3)	0.62 (0.40, 0.98)	0.0408	0.0394
Pembrolizumab 10 mg/kg Q3W	91	36 (39.6)	983.7	3.7	Not Reached (12.7, .)	83.3 (73.9, 89.6)	0.69 (0.44, 1.09)	0.1140	0.1130
Treatment-by-subgroup interaction							p-Value based on Q-statistic	I^2 statistic (%)	
Pembrolizumab 10 mg/kg Q2W vs. Ipilimumab 3 mg/kg							0.8297	0.00	
Pembrolizumab 10 mg/kg Q3W vs. Ipilimumab 3 mg/kg							0.9274	0.00	

[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Cox proportional hazard model stratified by ECOG performance status (0 vs. 1), PD-L1 expression (low vs. high), line of therapy (1 line vs. 2 line)
[§] Two-sided p-value based on Wald-test
[‖] Two-sided p-value based on log-rank test
(Database Cutoff Date: 03MAR2015)

Table 18: ORR by IRO per RECIST (%) by Gender (ITT Population)

Treatment	Gender		Treatment-by-subgroup †
	Male	Female	p-value
Ipilimumab 3 mg/kg	14.8	7.8	
Pembrolizumab 10 mg/kg Q2W	37.9	28.0	0.671
Pembrolizumab 10 mg/kg Q3W	39.1	22.3	0.146
† Pairwise (Pembrolizumab dose group versus control) treatment-by-subgroup interaction based on observed proportions			

Table 19: ORR by IRO per RECIST (%) by Age Group (ITT Population)

Treatment	Age Group		Treatment-by-subgroup †
	<65	>=65	p-value
Ipilimumab 3 mg/kg	9.0	16.1	
Pembrolizumab 10 mg/kg Q2W	30.7	37.3	0.949
Pembrolizumab 10 mg/kg Q3W	28.9	37.6	0.818
† Pairwise (Pembrolizumab dose group versus control) treatment-by-subgroup interaction based on observed proportions			

Table 20: ORR by IRO per RECIST (%) by Region (ITT Population)

Treatment	Region		Treatment-by-subgroup †
	United States	Other	p-value
Ipilimumab 3 mg/kg	10.9	12.1	
Pembrolizumab 10 mg/kg Q2W	36.0	33.2	0.644
Pembrolizumab 10 mg/kg Q3W	51.1	29.1	0.011
† Pairwise (Pembrolizumab dose group versus control) treatment-by-subgroup interaction based on observed proportions			

Table 21: ORR by IRO per RECIST (%) by ECOG Performance Status at Screening (ITT Population)

Treatment	ECOG Performance Status at Screening		Treatment-by-subgroup †
	0	1	p-value
Ipilimumab 3 mg/kg	13.3	8.9	
Pembrolizumab 10 mg/kg Q2W	38.3	22.9	0.115
Pembrolizumab 10 mg/kg Q3W	33.9	30.7	0.864
† Pairwise (Pembrolizumab dose group versus control) treatment-by-subgroup interaction based on observed proportions			

Table 22: ORR by IRO per RECIST (%) by PDL1 (ITT Population)

Treatment	PD-L1 subgroup		Treatment-by-subgroup †
	PD-L1 Positive	PD-L1 Negative	p-value
Ipilimumab 3 mg/kg	12.4	10.6	
Pembrolizumab 10 mg/kg Q2W	38.2	16.3	0.012
Pembrolizumab 10 mg/kg Q3W	36.7	18.5	0.041
† Pairwise (Pembrolizumab dose group versus control) treatment-by-subgroup interaction based on observed proportions			

Table 23: ORR by IRO per RECIST (%) by BRAF status (ITT Population)

Treatment	BRAF status			Treatment-by-subgroup †
	Wild-type	Mutant, anti-BRAF	Mutant, no anti-BRAF	p-value
Ipilimumab 3 mg/kg	12.9	5.8	12.7	
Pembrolizumab 10 mg/kg Q2W	33.9	25.6	40.0	0.749
Pembrolizumab 10 mg/kg Q3W	34.3	15.9	41.5	0.163
† Pairwise (Pembrolizumab dose group versus control) treatment-by-subgroup interaction based on observed proportions				

Table 24: ORR by IRO per RECIST (%) by Line of Systemic Therapy (ITT Population)

Treatment	Line of Systemic Therapy		Treatment-by-subgroup †
	First Line	Second Line	p-value
Ipilimumab 3 mg/kg	12.2	11.3	
Pembrolizumab 10 mg/kg Q2W	36.1	29.2	0.391
Pembrolizumab 10 mg/kg Q3W	38.4	22.0	0.024
† Pairwise (Pembrolizumab dose group versus control) treatment-by-subgroup interaction based on observed proportions			

A9. **Table 37 of the company submission provides results for key efficacy endpoints for KEYNOTE-006; both arms are labelled as pembrolizumab 10 mg/kg Q3W. Please provide an updated table in order to indicate which results are for the pembrolizumab 10 mg/kg Q3W arm, and which are for the pembrolizumab 2 mg/kg arm.**

An updated version of Table 37 from page 97 of MSD original submission [ID801] document is provided below (

Table 25):

Table 25: Cross-study comparison of key efficacy endpoints by dose level in KEYNOTE-001 Part D and KEYNOTE-006

	KEYNOTE-001 (Part D)		KEYNOTE-006	
	2 mg/kg Q3W	10 mg/kg Q3W	10 mg/kg Q3W	10 mg/kg Q2W
ORR (%)	33	35	33	34
PFS (median, mo)	5.5	4.2	4.1	5.5
6-month PFS rate (%)	50	41	46	47
OS (median)	not reached	not reached	not reached	not reached
12-month OS rate (%)	72	64	68	74

A10. **On page 111 of the company submission, it is stated that "KEYNOTE-006 first-line subgroup has 0%; KEYNOTE-006 second-line subgroup has 100%". Please clarify what is meant by this statement given that in the network meta-analysis network of evidence (company submission, pages 112–113) it is shown that KEYNOTE-006 includes both first- and second-line patients.**

In scenario 3a and 3b the evidence networks consist of studies evaluating first line systemic treatment (i.e. no history of systematic treatment), studies evaluating second-line systemic treatment, and studies with a mixed distribution [i.e. Hersh *et al* (2011) and Haushield *et al* (2012; BREAK-3)]. Unlike for all other studies in the networks, for Keynote-006 MSD had access to subgroup data by line of treatment. As such, we included both the KM data of first line and second line treatment in the data set with covariate values set at 0 and 100%, respectively. This provided more contrast in the data set and therefore more stable and accurate estimates of the difference between first and second line treatment regarding treatment effects in terms of the scale parameter (which was assumed constant across all interventions relative to ipilimumab).

The model used for the analysis of time to event outcomes for scenario 3a and 3b is presented here below, with power p set to 0 (i.e. a Weibull model). Variable X_j reflects the proportion of patients with a history of systemic treatment, as defined in the data set used for the analyses. As such, the obtained parameter estimates d_0 and d_1 reflect the relative treatment effect in terms of scale and shape of ln-hazard function when X=0, i.e. for a population without a history of systemic treatment. With this model the covariate is assumed to only affect the treatment effect in terms of scale. This implies that the treatment effect in terms of shape is the same for both the first and second line setting (if no subgroup specific data has been available). The treatment effect in terms of scale for the second line setting equals $d_0+\beta$. Alternatively, one can run the model with the same dataset but now defining X_j as the proportion of patients without a history of systemic treatment and the parameter

estimate d_0 reflects the treatment effect in terms of scale when X=0, i.e. a population with a history of systemic treatment.

$$\ln\left(h_{jkt}\right)=\beta_{0jk}+\beta_{1jk}t^{p} \qquad \text{with } t^{0}=\log(t), \quad p\in\{0,1\}$$

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\end{pmatrix}=\begin{cases}\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix} & \text{if } k=b, b\in\{A,B,C\}\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}+\begin{pmatrix}d_{0Ak}-d_{0Ab}+\beta X_j\\ d_{1Ak}-d_{1Ab}\end{pmatrix} & \text{if } k\succ b \text{ and } b=A\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}+\begin{pmatrix}d_{0Ak}-d_{0Ab}\\ d_{1Ak}-d_{1Ab}\end{pmatrix} & \text{if } k\succ b \text{ and } b\neq A\end{cases} \qquad (1)$$

A11. **Please provide further information as to why the Weibull model was chosen as the most appropriate survival model for the network meta-analysis. Specifically, please provide a list of the survival models used for the network meta-analysis, results of the assessments of goodness of fit for each of these models, and further explanation as to why the Weibull provided "plausible extrapolation of relative treatment effects beyond the trial follow-periods available" (company submission, page 121).**

The survival models used for the network meta-analysis and the results of the assessment of goodness of fit for each model are provided in an excel file attached to this response.

MSD used multivariate network meta-analysis models to estimate relative treatment effects. The following fixed effects model assumes a treatment effect in terms of scale (β_0) and shape (β_1) of the ln-hazard function. When we set p=0 this model represents Weibull distributed survival times and with p=1 the model represents Gompertz distributed survival times.

$$\ln\left(h_{jkt}\right)=\beta_{0jk}+\beta_{1jk}t^{p} \qquad \text{with } t^{0}=\ln(t)$$

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\end{pmatrix}=\begin{cases}\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix} & k=b, b\in\{\mathrm{A},\mathrm{B},\mathrm{C},\ldots\}\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}+\begin{pmatrix}d_{0Ak}-d_{0Ab}\\ d_{1Ak}-d_{1Ab}\end{pmatrix} & \text{if } k\succ b\end{cases} \qquad (2)$$

A disadvantage of this model is that it can only represent monotonic increasing or decreasing ln-hazard functions over time. As such, we evaluated also more flexible models that can capture changes in direction of the hazard function. The most flexible models we used assumed that the ln-hazard function can be described with a 2nd order fractional polynomial and treatment has an impact on 1 scale and 2 shape parameters:

$$\ln\left(h_{jkt}\right)=\begin{cases}\beta_{0jk}+\beta_{1jk}t^{p_1}+\beta_{2jk}t^{p_2} & p_1\neq p_2\\ \beta_{0jk}+\beta_{1jk}t^{p}+\beta_{2jk}t^{p}\ (\log t) & p=p_1=p_2\end{cases}\qquad \text{with } t^0=\ln t$$

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\\ \beta_{2jk}\end{pmatrix}=\begin{cases}\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix} & k=b, b\in\{\mathrm{A},\mathrm{B},\mathrm{C},...\}\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix}+\begin{pmatrix}d_{0Ak}-d_{0Ab}\\ d_{1Ak}-d_{1Ab}\\ d_{2Ak}-d_{2Ab}\end{pmatrix} & \text{if } k\succ b\ .\end{cases}\qquad (3)$$

Out of all the possible values for p_1 and p_2 (-2, -1, -0.5, 0, 0.5, 1, 2) we only evaluated the combinations p_1=0, p_2=1 and p_1=1, p_2=0 which generally provide the most stable results. However, this model with treatment effects for 1 scale (d_0) and 2 shape parameters (d_1 and d_2) did not provide stable estimates. In attempt to obtain more stable estimates while still capturing possible changes in direction of the hazard function, we removed the third treatment effect parameter (d_2) thereby assuming that treatment only impacts β_0 and β_1:

$$\ln\left(h_{jkt}\right)=\begin{cases}\beta_{0jk}+\beta_{1jk}t^{p_1}+\beta_{2jk}t^{p_2} & p_1\neq p_2\\ \beta_{0jk}+\beta_{1jk}t^{p}+\beta_{2jk}t^{p}\ (\log t) & p=p_1=p_2\end{cases}\qquad \text{with } t^0=\ln t$$

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\\ \beta_{2jk}\end{pmatrix}=\begin{cases}\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix} & k=b, b\in\{\mathrm{A},\mathrm{B},\mathrm{C},...\}\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix}+\begin{pmatrix}d_{0Ak}-d_{0Ab}\\ d_{1Ak}-d_{1Ab}\\ 0\end{pmatrix} & \text{if } k\succ b\ .\end{cases}\qquad (4)$$

These models provided better fit to the data and smaller DIC estimates than the Weibull and Gompertz equivalent mentioned above. However, the parameter estimates were rather uncertain providing very wide credible intervals (CrI) of the hazard ratio (HR) for longer follow-up time points. In addition, when we transformed the HR function over time into modelled PFS and OS curves by treatment (assuming the same 2nd order fractional polynomial for the reference intervention ipilimumab) we obtained "horizontal" extrapolations for PFS and OS, which seems unrealistic. In short, the flexible second order fractional polynomial models did not provide sufficiently stable estimates for realistic extrapolation. Please note, that these models do capture similar survival functions as the lognormal and log-logistic distributions.

That leaves the Weibull and Gompertz equivalents of the 1st order fractional polynomial models (eq. 2). Although the Gompertz model fitted the data better than a Weibull (based on DIC), the issue with the Gompertz model was that it describes the ln-HR as linear function of time (rather than ln(time) as with the Weibull) resulting in very uncertain HR estimates near the end of the follow-up period which translated in unrealistic wide CrI for the corresponding extrapolated PFS and OS curves. As such, we opted to use the Weibull model to estimate relative treatment effects between interventions included in the network meta-analysis. The relative treatment effects vary over time according to: $\ln(HR(t)) = d_{0Ak} + d_{1Ak} \ln(t)$.
We have attached an excel document with an overview of the different models evaluated for each scenario along with model fit estimates and plots of the HR over time and corresponding PFS and OS curves assuming the baseline treatment ipilimumab follows the same survival function as used for the relative treatment effects.

A12. **NMAs were performed for four scenario networks to provide results for the outcomes of PFS and OS. OS results were generated only for scenario 3a. The ERG assumes that this is because Hersh et al do not provide PFS curves; however, for scenario 1, PFS data for Hersh et al were generated using the OS data and the relationship between HR PFS and HR OS based on a method described by Flaherty et al. (2014). The ERG would like to request clarification as to why the Flaherty method was not used to provide PFS results for Hersh et al for scenario 3a**

In scenario 1, the trial by Hersh *et al* was used to have a connection in the network between DTIC and ipilimumab. In the absence of PFS data for Hersh *et al* there would not be a connected network under scenario 1 if PFS would not be predicted for this trial. Under scenario 3a on the other hand, there is a connection between DTIC and ipilimumab given the presence of the study by Hodi *et al* (2010) (after adjustment for line of treatment) and Hersh *et al* is no longer needed. Without Hersh *et al* in the network for PFS we in essence have scenario 3b. As such, no results were reported for PFS under scenario 3a.

As stated in the report, of the four different scenarios (1, 2, 3a and 3b), scenarios 2 and 3b are likely the most trustworthy because the trial by Hersh *et al* was not included in those. In addition to the lack of PFS results, the trial by Hersh *et al* also allowed crossover between treatment groups (unlike other trials used for the wild type population) which could not be adjusted for with data available. Any projection of PFS treatment effects based on reported OS (unadjusted for cross-over) using the Flaherty method is possibly biased.

Section B: Clarification on cost-effectiveness data

B1. Please explain the treatment pathway for patients who were allocated to the ipilimumab arm of the KEYNOTE-006 trial but withdrew from the trial before receiving a single dose of ipilimumab. Please also explain precisely how such patients have been accounted for in the analyses.

For the estimation of the drug utilisation and the corresponding drug cost calculation for pembrolizumab and ipilimumab, only "treated" patients were included in the analysis. Patients not initially treated with ipilimumab were not considered in the model since the model aimed to reflect patients initially treated with pembrolizumab compared to patients treated with any of the relevant comparators. Therefore, the purpose of the drug utilisation analysis conducted on the basis of the KEYNOTE-006 trial data was to estimate the drug cost of and compliance with pembrolizumab and ipilimumab among all the patients who had initiated treatment.

The KEYNOTE-006 CSR establishes that: 'There were 22 subjects in the IPI arm and 1 subject in the MK-3475 (pembrolizumab) 10 mg/kg Q2W arm that were randomized but not treated with study drug as the majority withdrew consent.' The majority of these patients withdrew from the study within the first week of the trial. The open label nature of the randomised allocation of patients within the KEYNOTE-006 trial is seeing as the main reason for the different withdrawal rates observed between the ipilimumab and the pembrolizumab treatment arms. On this basis, we decided not to run additional survival analyses considering efficacy estimates based on the per-protocol data since this additional analysis was viewed as irrelevant from the point of view of cost-effectiveness decision-making.

B2. Please provide the following Kaplan-Meier analyses (listed in a. to e. below) to the following specification:

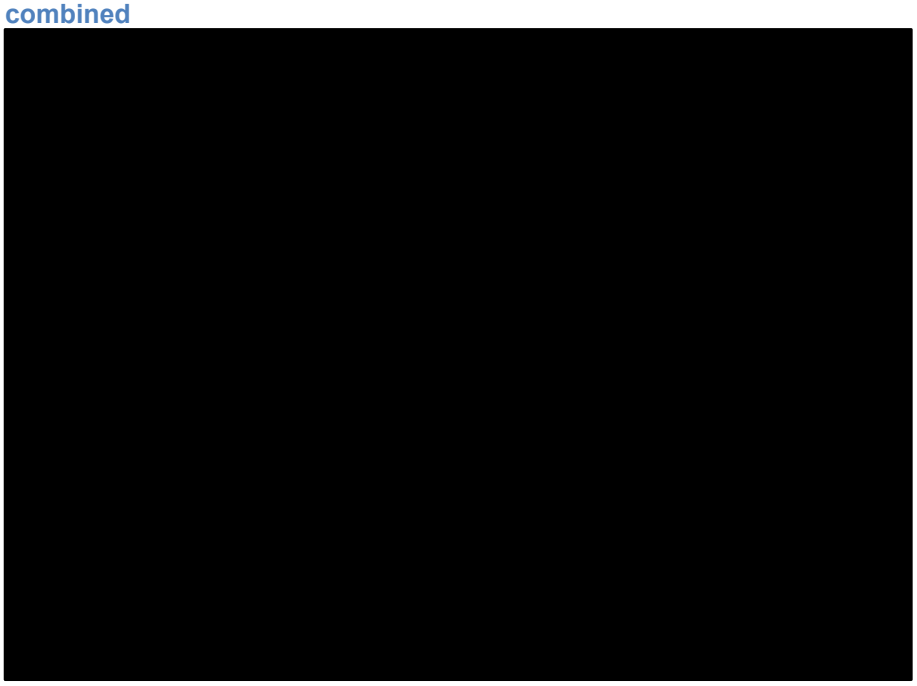
Population: The per protocol population, including all patients lost to follow-up or withdrawing from the trial.

Censoring: Censor lost to follow-up and withdrawn patients at the time recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, and not when last seen. Please use the format of the table provided below.

Trial data set: KEYNOTE-006, latest data cut.

a. Time to death from any cause (overall survival) Kaplan-Meier analysis for both of the pembrolizumab 10 mg/kg treatment arms (Q2W and Q3W) separately and combined (3 analyses)

Figure 1. KM for OS: pembrolizumab 10 mg/kg treatment arms (Q2W and Q3W) separately and combined



In the tables below, to match SAS output, the first column time is "Time in Weeks"; the second one "n.risk" is "Number Left"; the third one "n.event" is "Number Failed", the fourth column relates to survival and the last one "std.err" is "Survival Standard Error".

Table 26. KM for OS for the pembrolizumab 10 mg/kg Q3W treatment arm

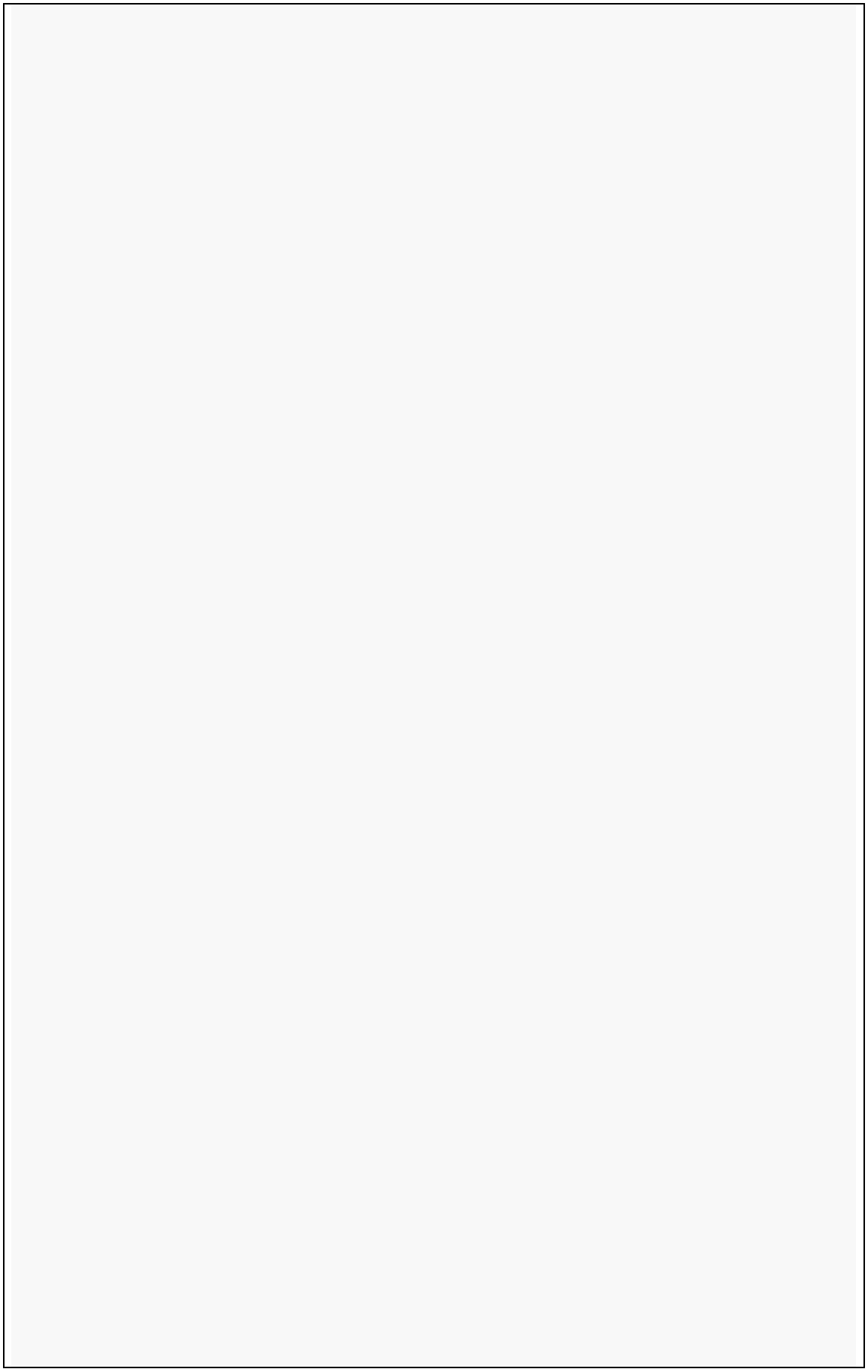
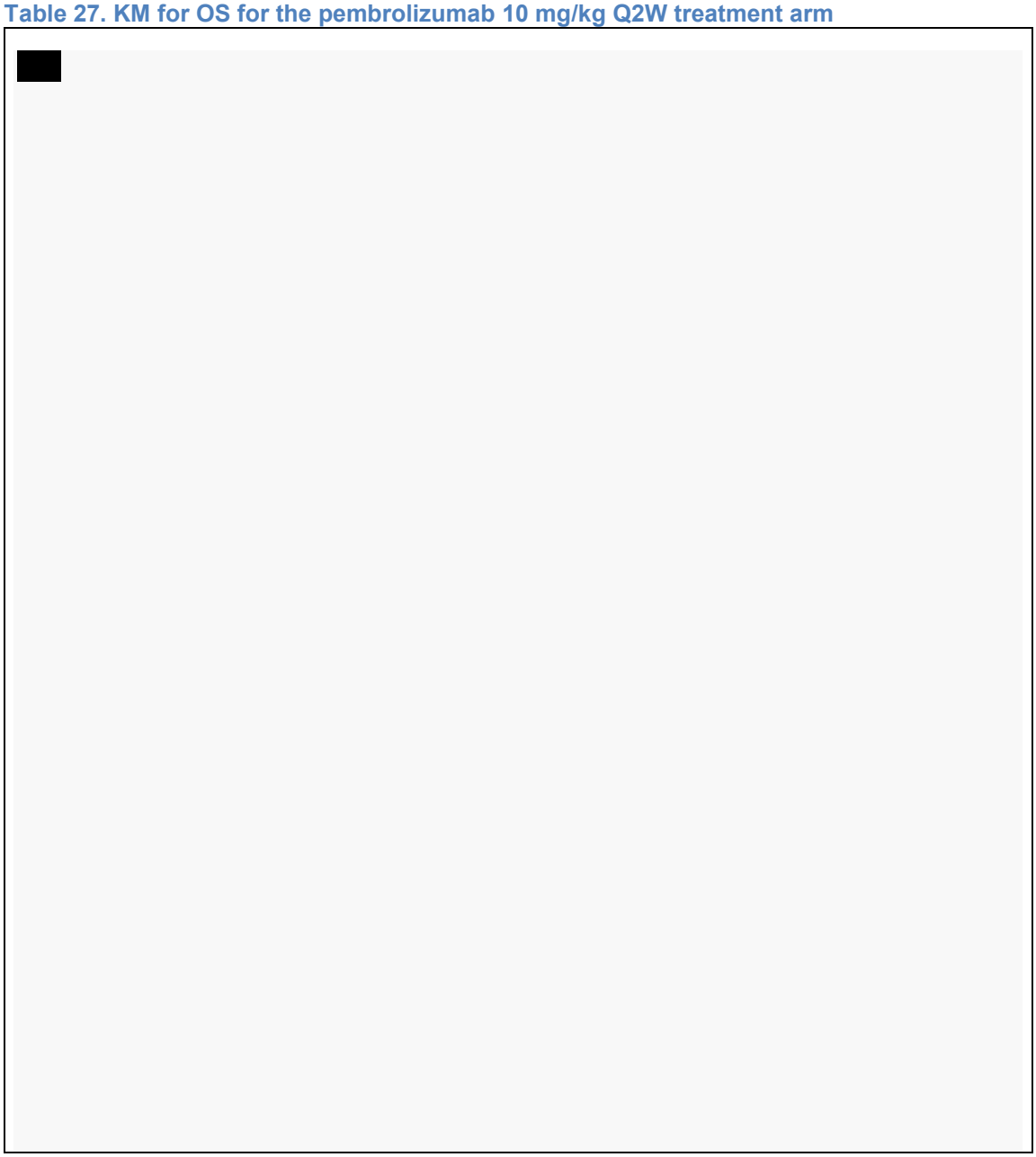


Table 27. KM for OS for the pembrolizumab 10 mg/kg Q2W treatment arm



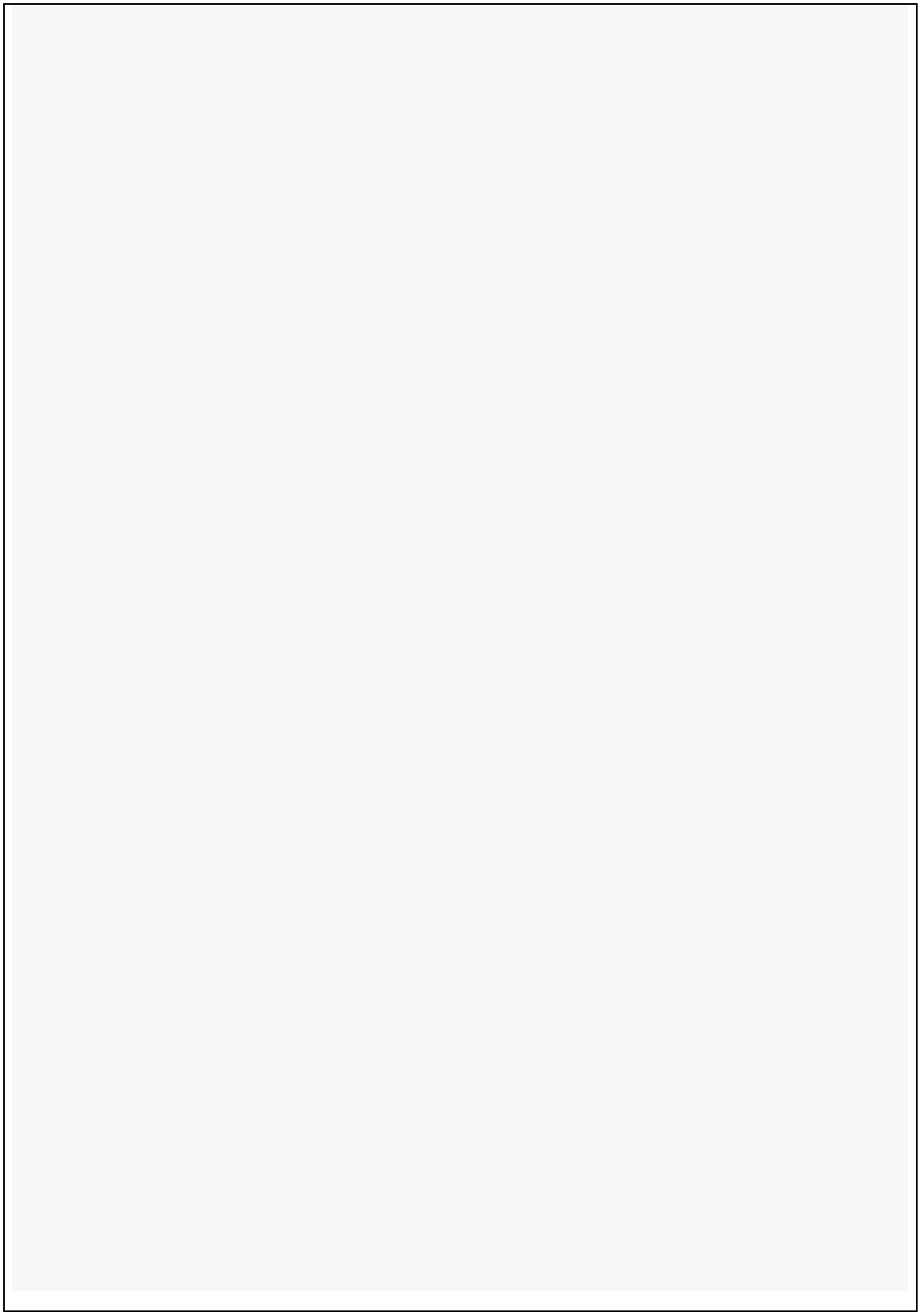
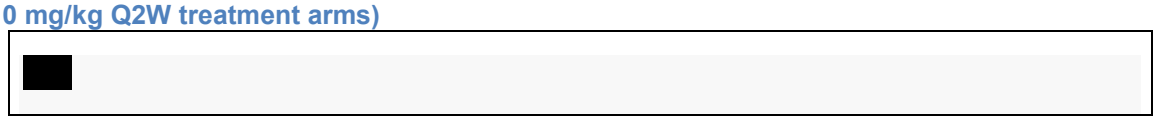
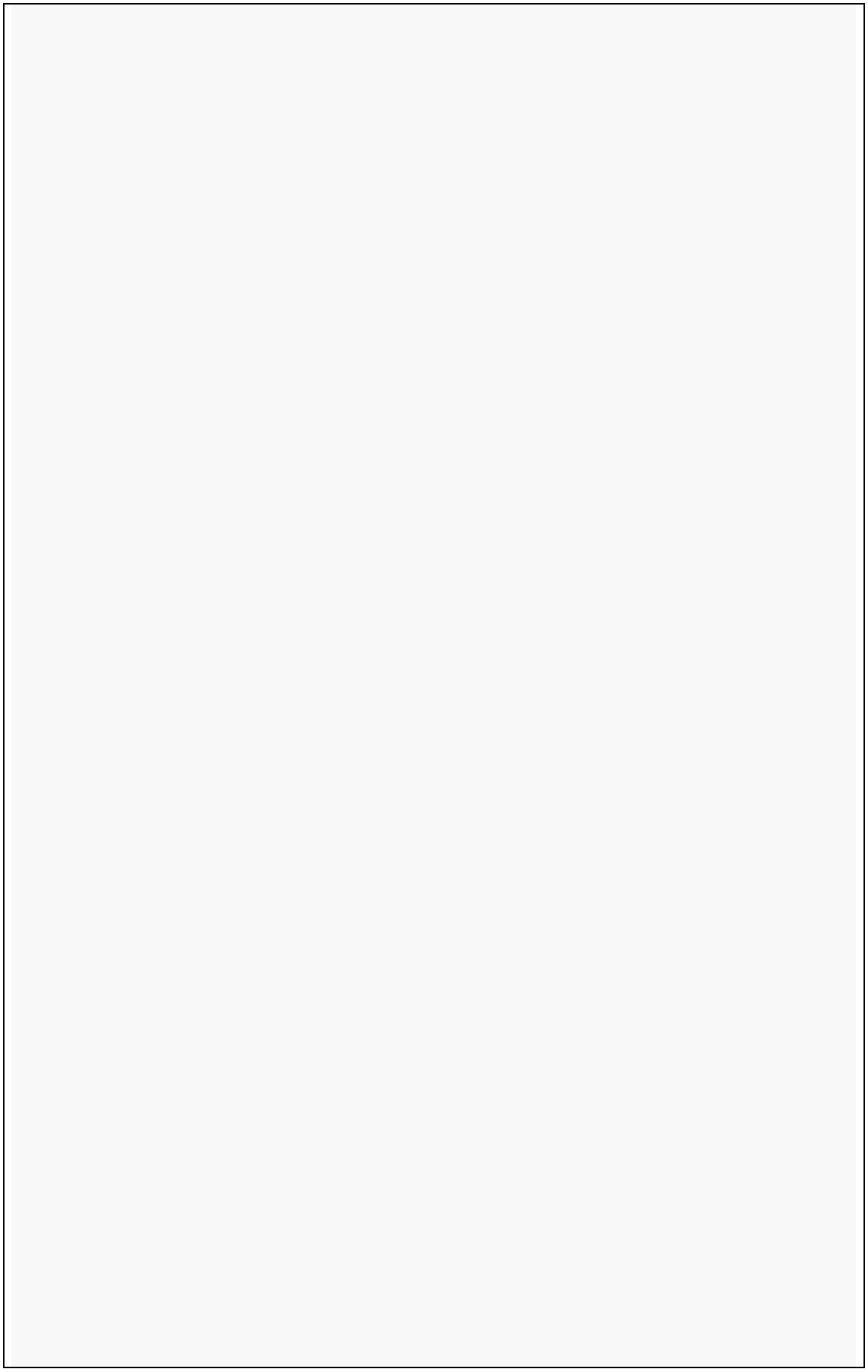
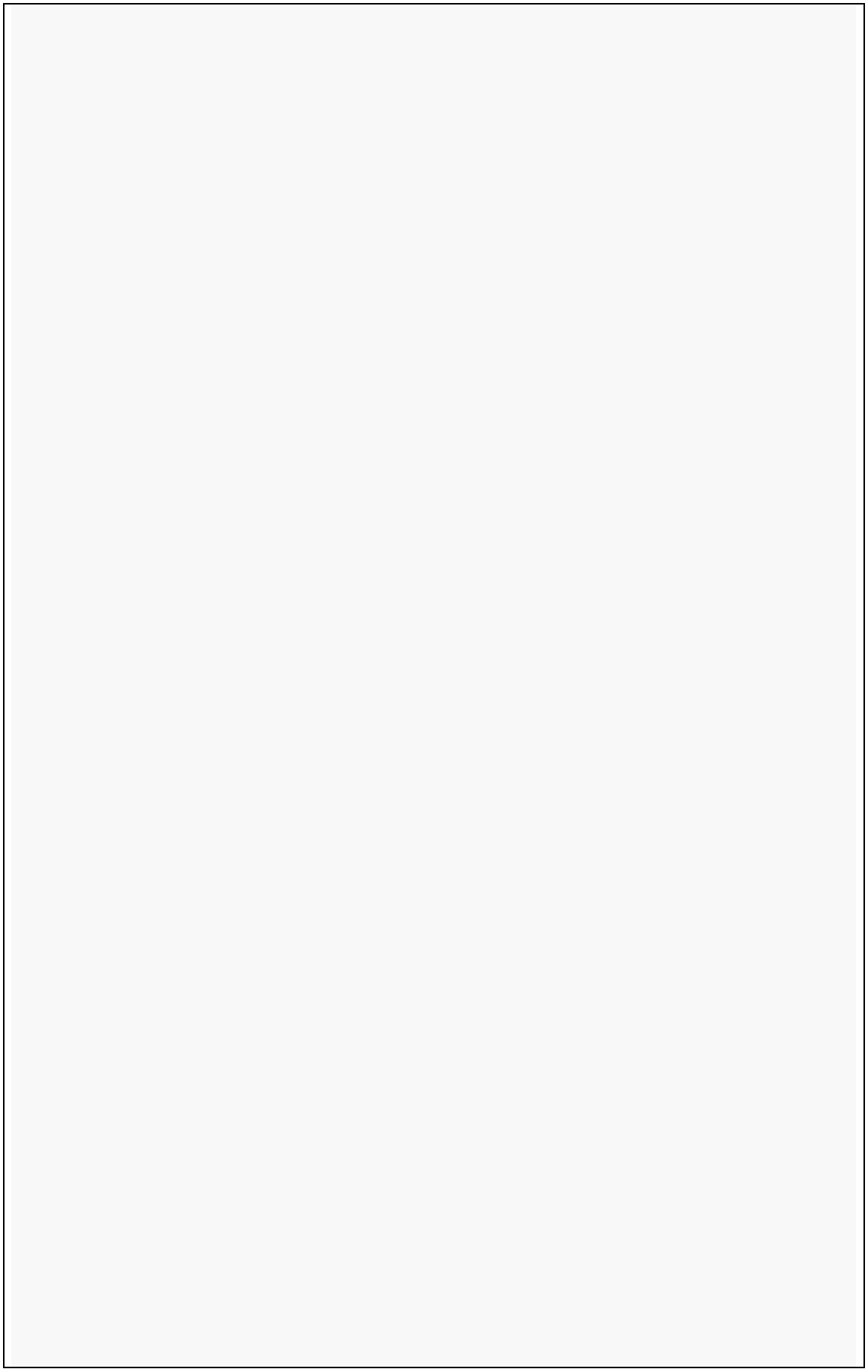
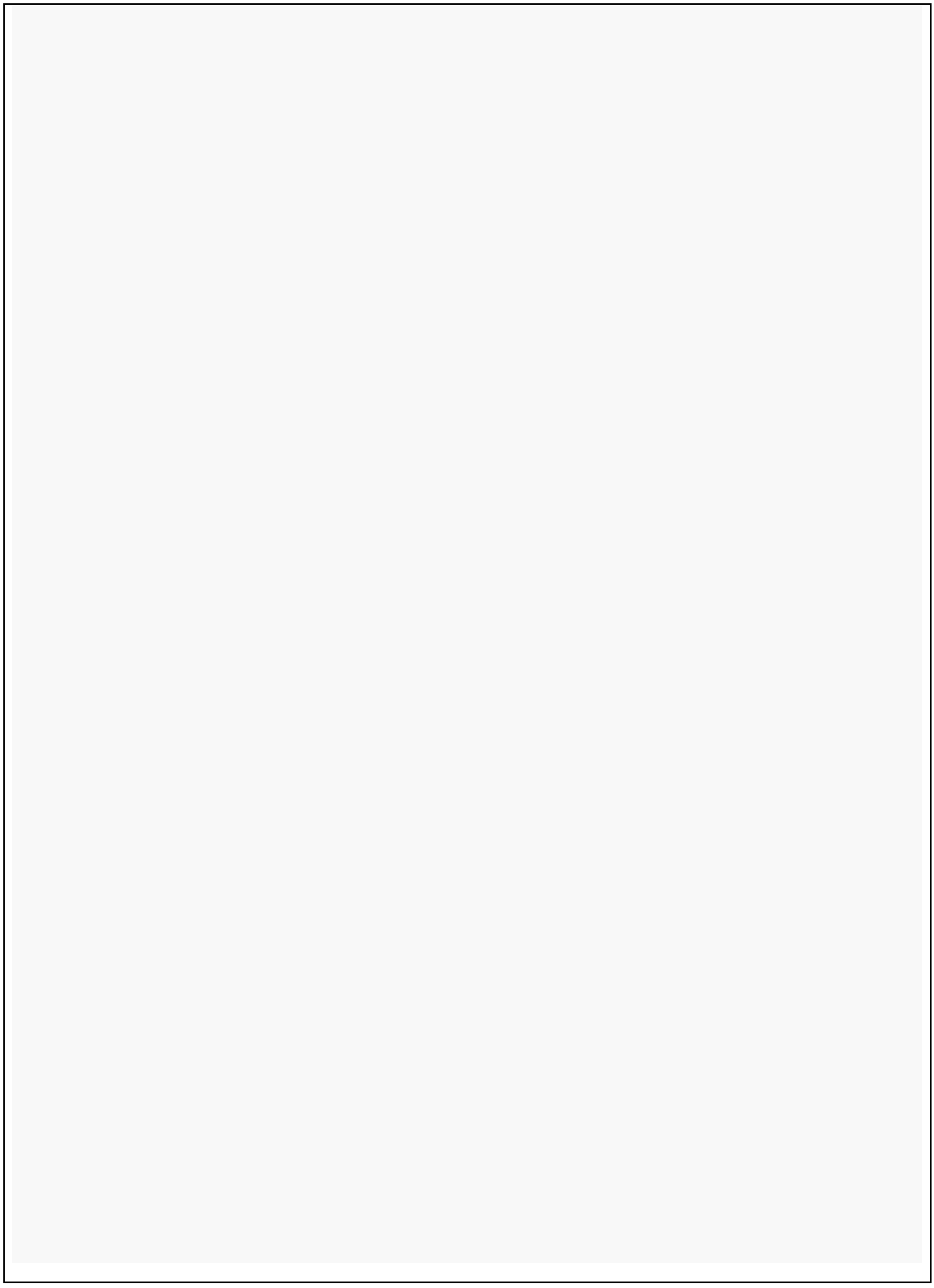


Table 28. KM for OS for the pembrolizumab combined treatment arms (i.e. 10 mg/kg Q3W and 10 mg/kg Q2W treatment arms)



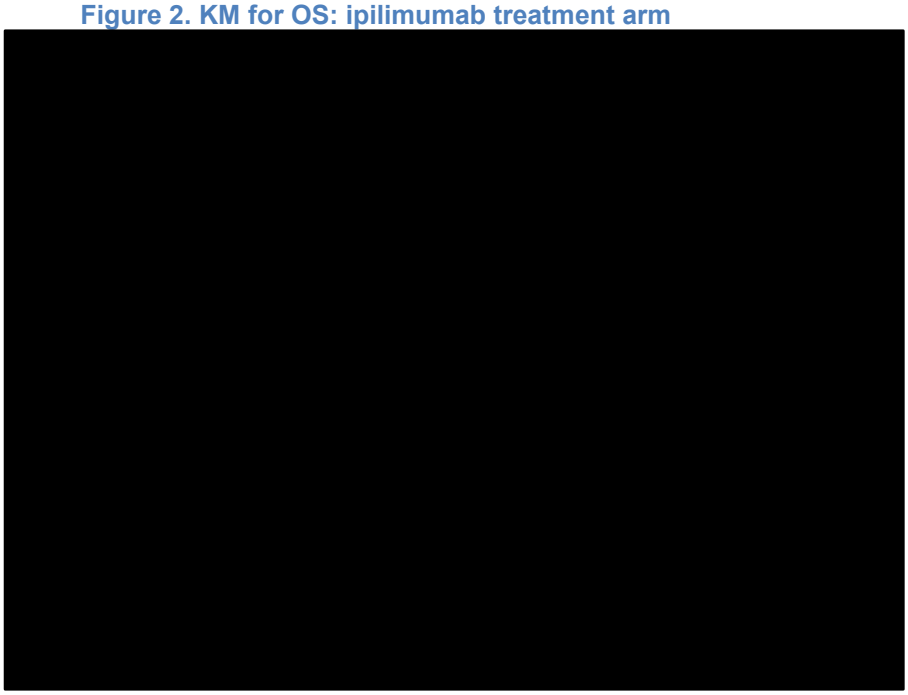






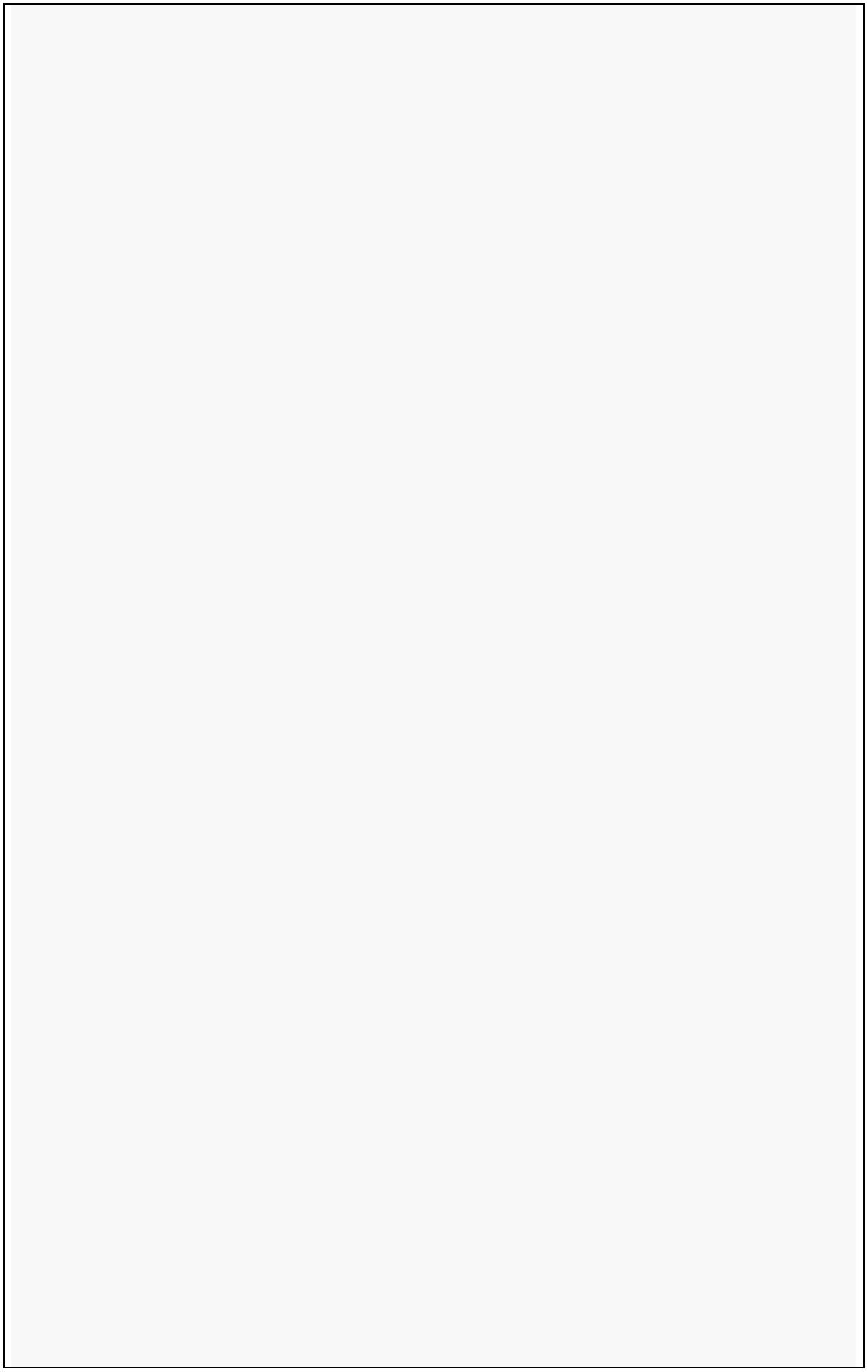
b. Time to death from any cause (overall survival) Kaplan-Meier analysis for the ipilimumab arm (1 analysis)

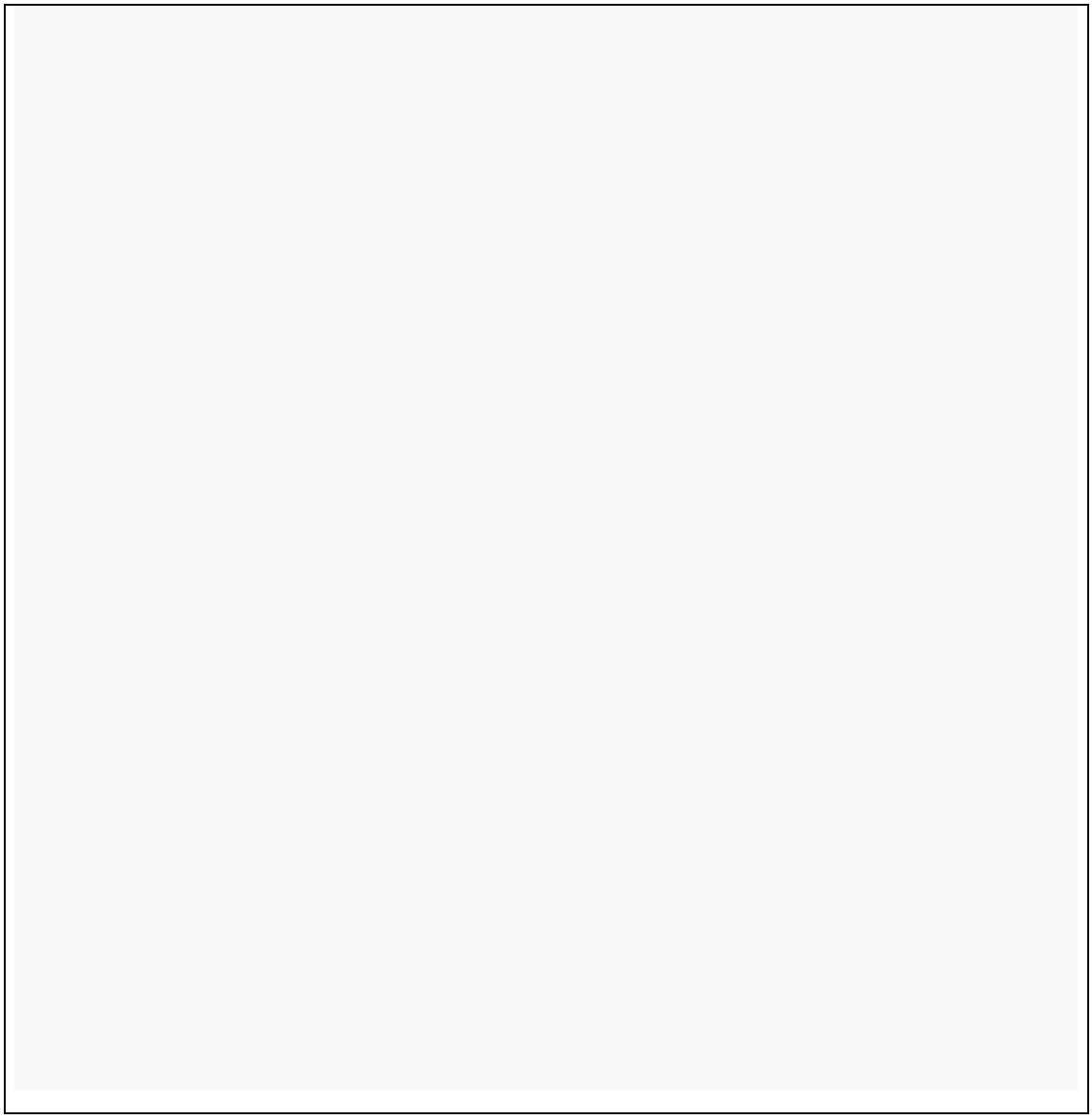
Figure 2. KM for OS: ipilimumab treatment arm



In the tables below, to match SAS output, the first column time is "Time in Weeks"; the second one "n.risk" is "Number Left"; the third one "n.event" is "Number Failed", the fourth column relates to survival and the last one "std.err" is "Survival Standard Error".

Table 29. KM for OS for the ipilimumab treatment arm





c. Time from disease progression by investigator assessment to death from any cause (post-progression survival) Kaplan-Meier analysis for the pembrolizumab arms (both arms separately and combined) and the ipilimumab arm (4 analyses)

Figure 3. KM for post-progression survival: for the pembrolizumab (10 mg/kg Q3W, 10 mg/kg Q2W and combined) and the ipilimumab treatment arms

Table 30. KM for post-progression survival for the pembrolizumab 10 mg/kg Q3W treatment arm

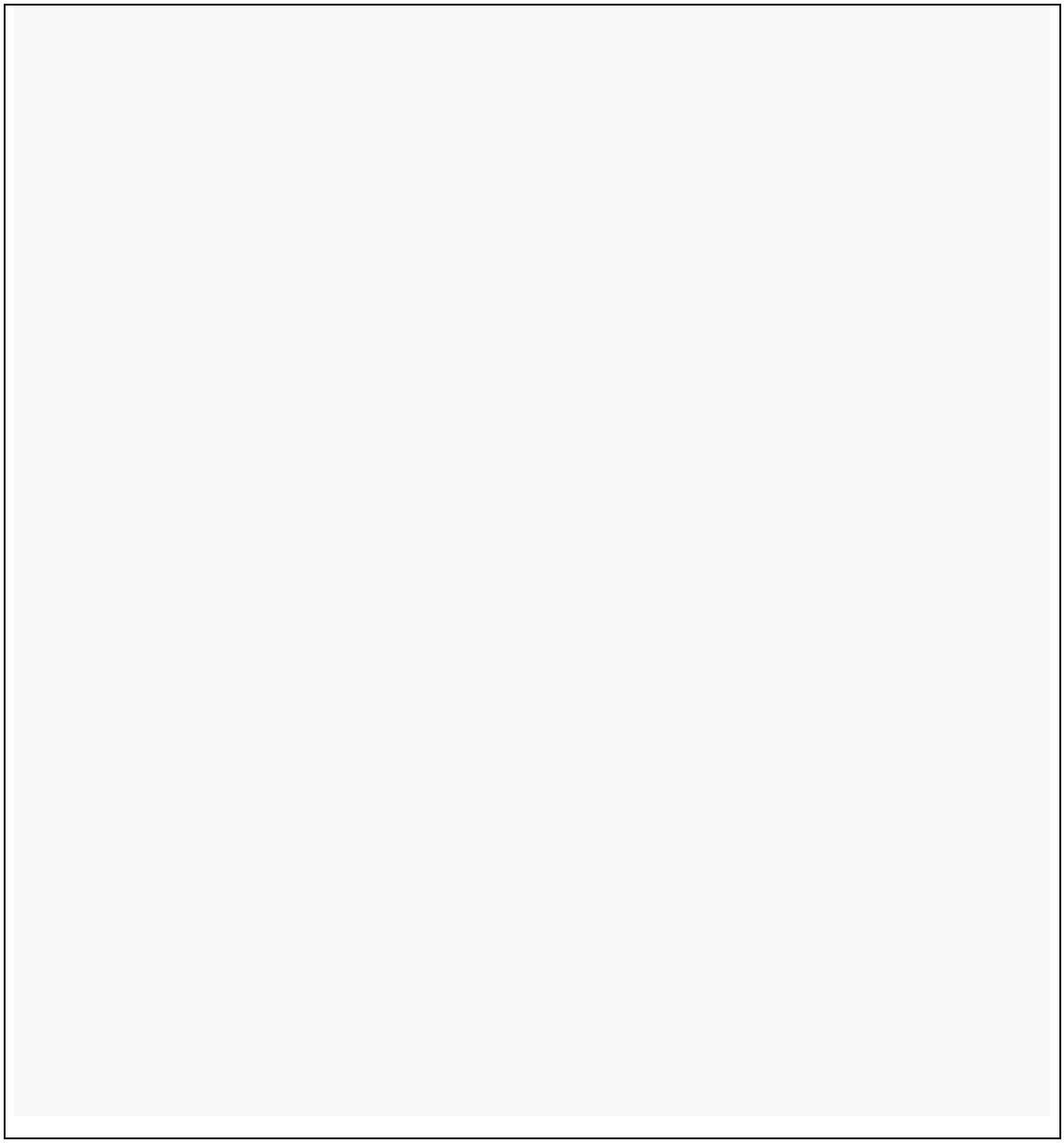


Table 31. KM for post-progression survival for the pembrolizumab 10 mg/kg Q2W treatment arm

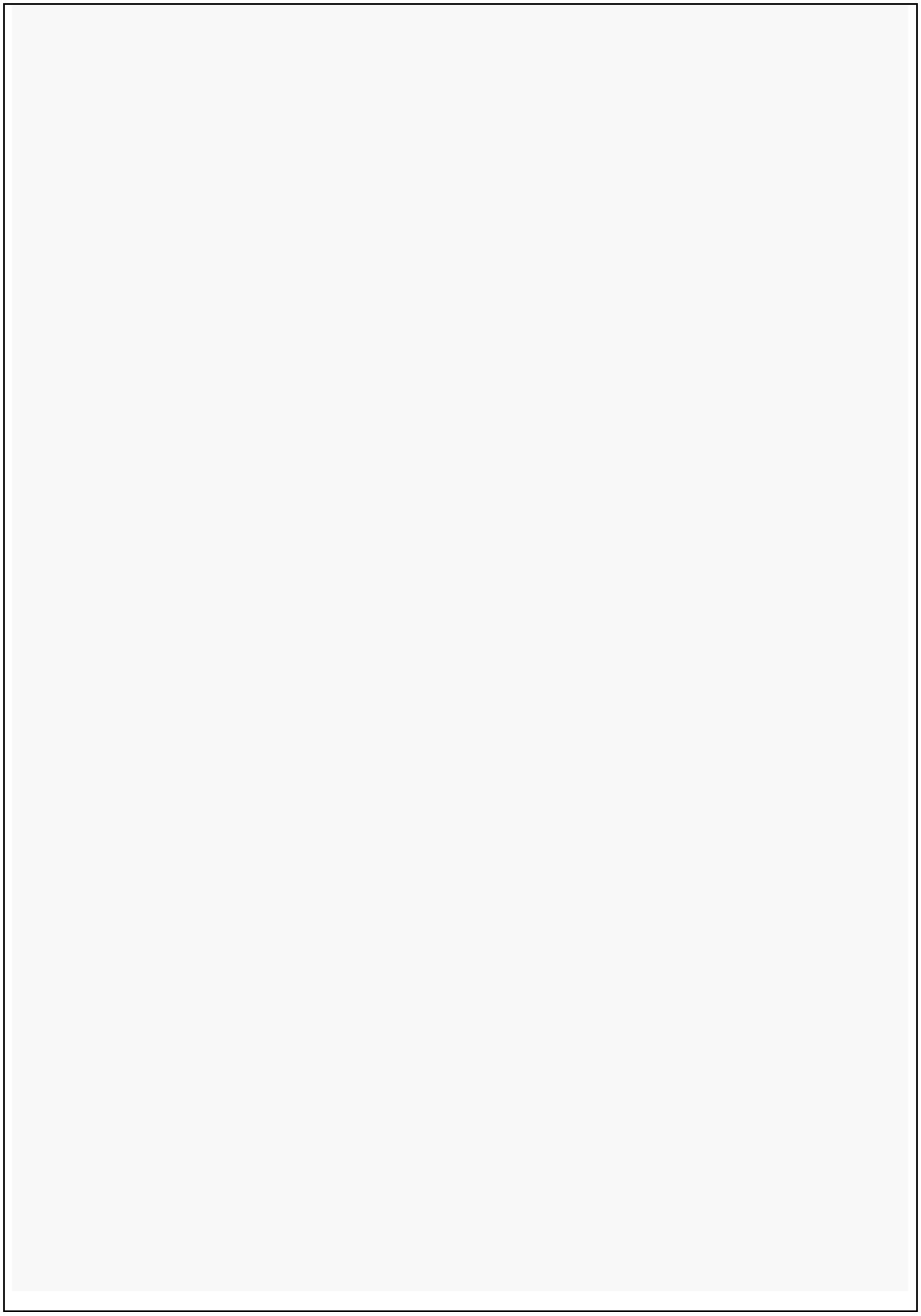
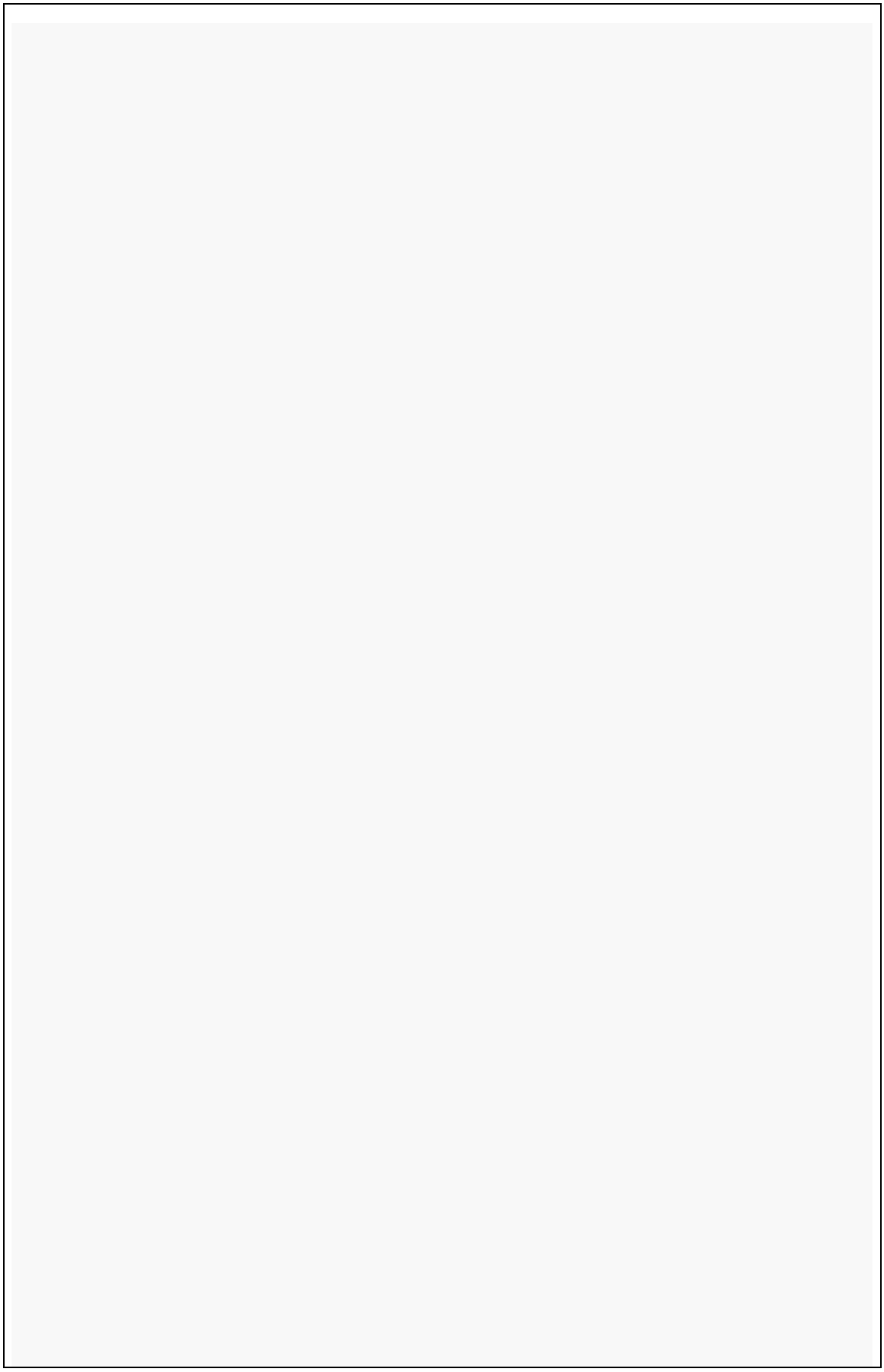


Table 32. KM for post-progression survival for the pembrolizumab 10 mg/kg Q3W and Q2W treatment arms combined



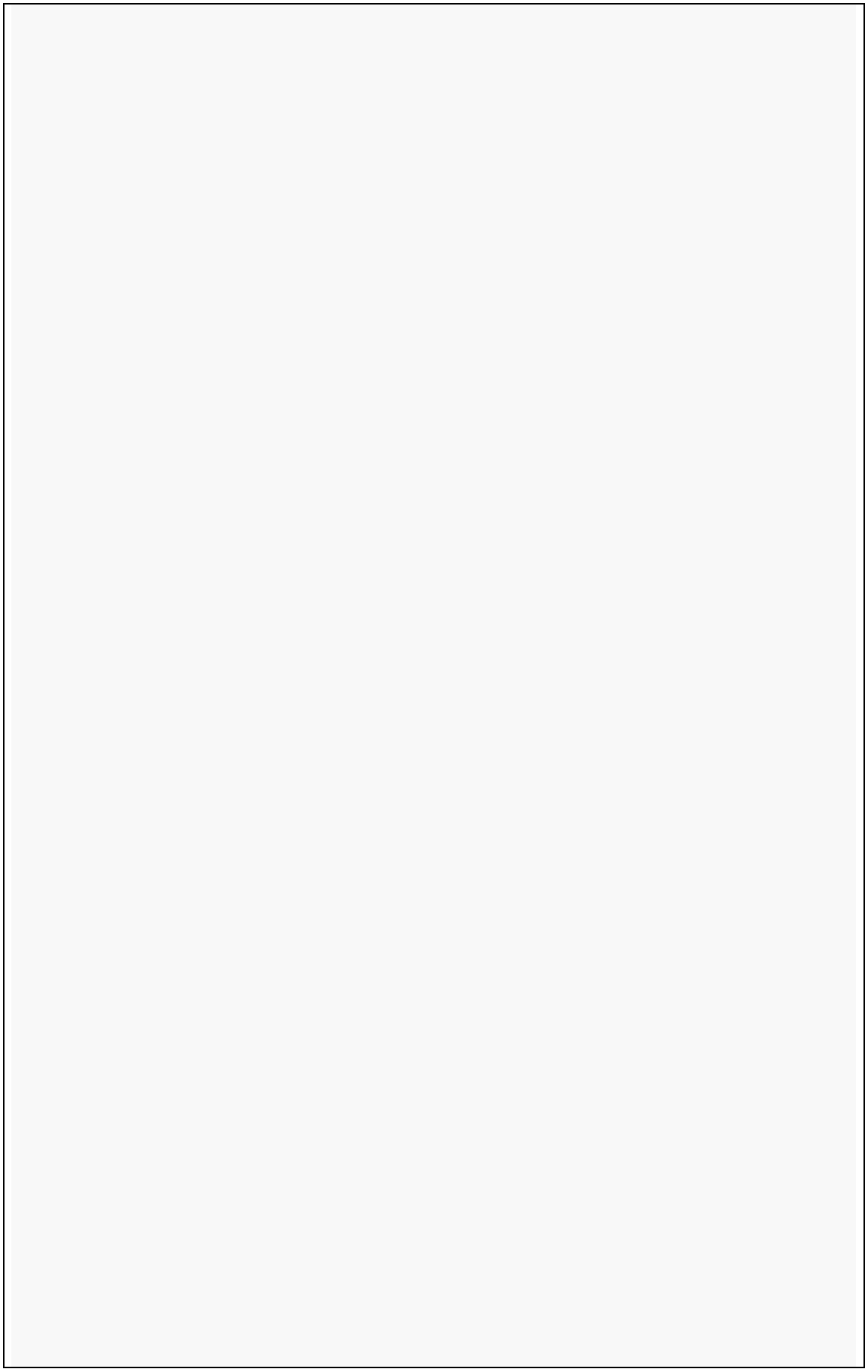
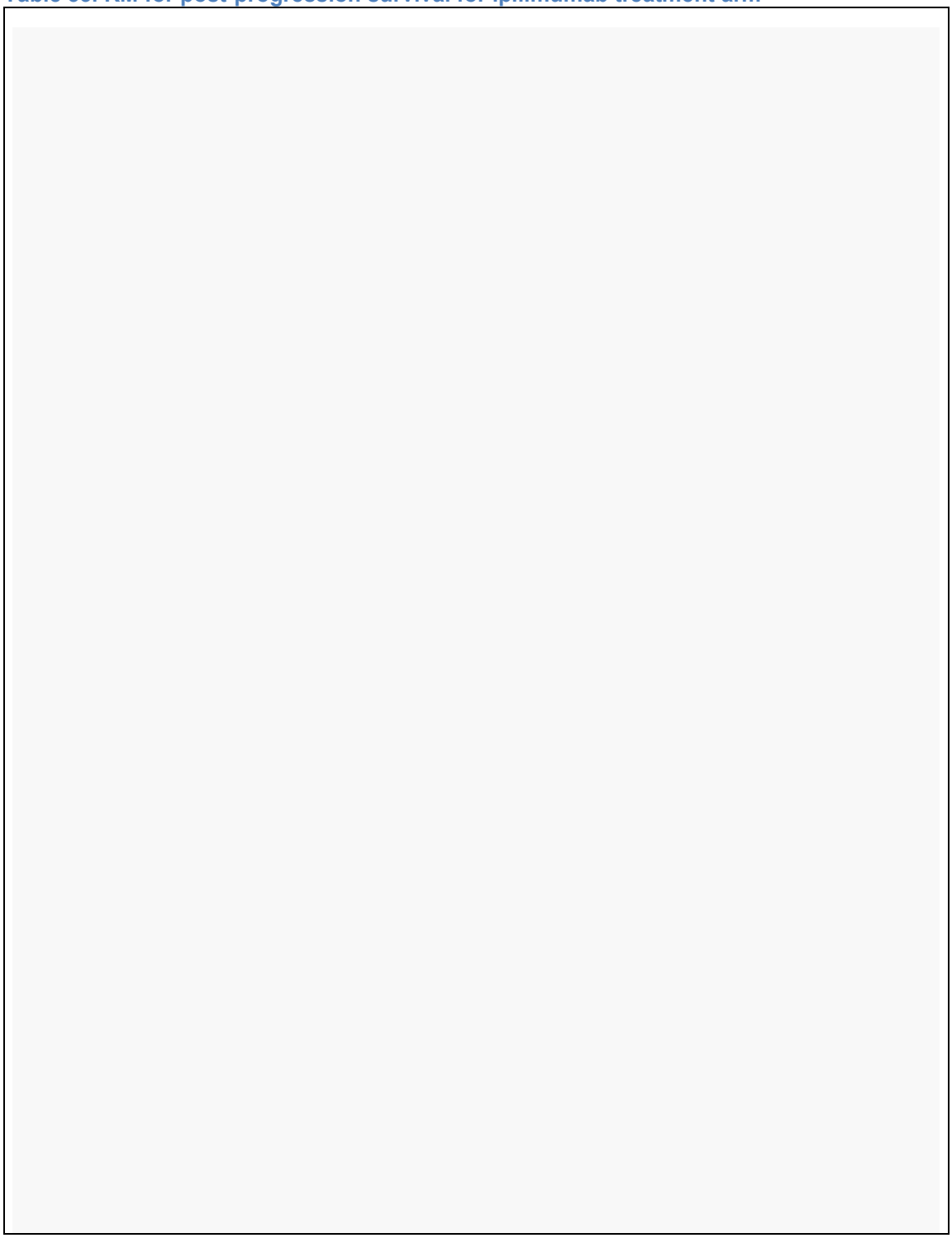
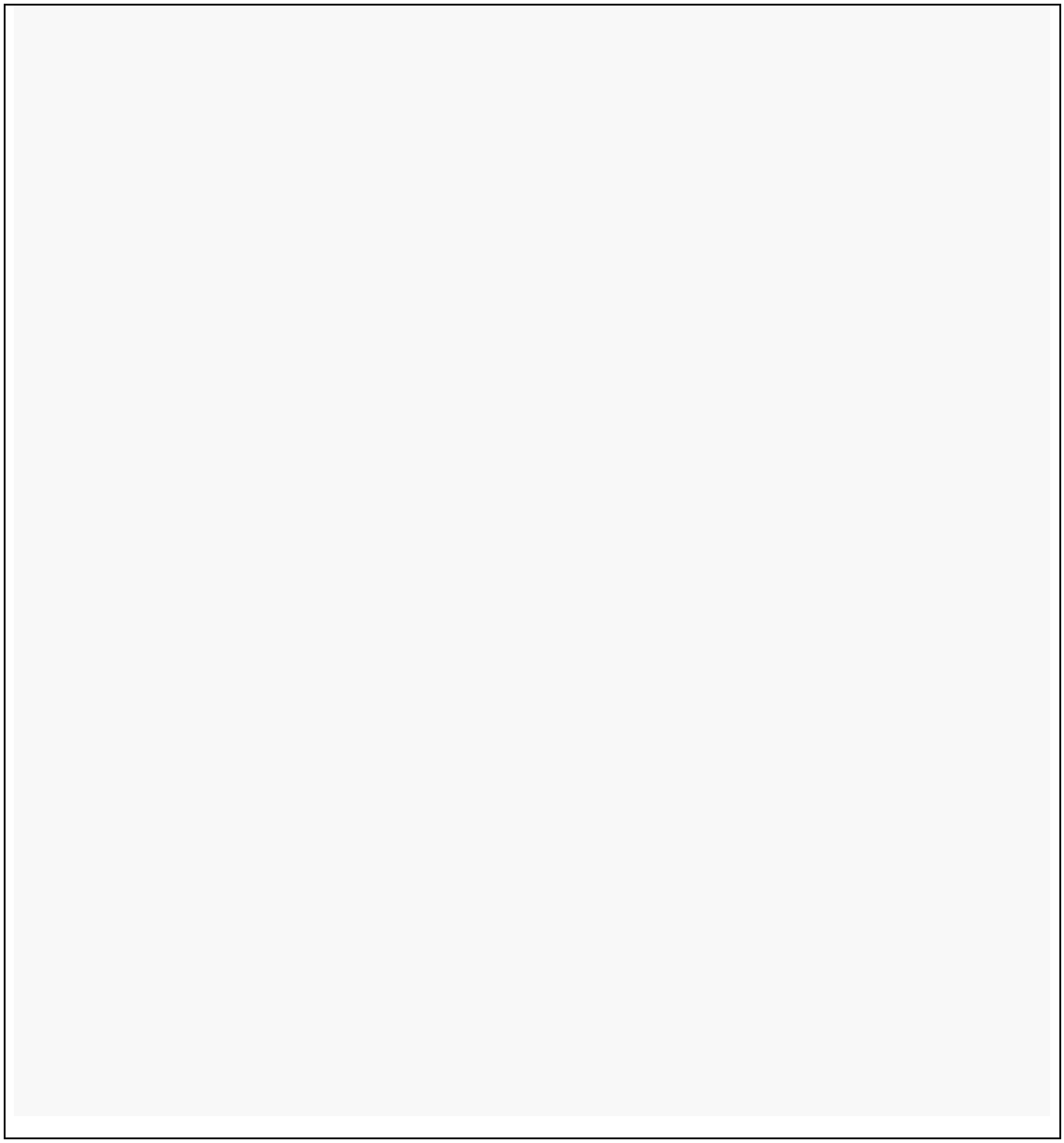


Table 33. KM for post-progression survival for ipilimumab treatment arm





d. Time to treatment discontinuation Kaplan-Meier analysis for both pembrolizumab arms (separately and combined) and the ipilimumab arm (4 analyses)

Figure 4. Time to treatment discontinuation for the pembrolizumab (10 mg/kg Q3W, 10 mg/kg Q2W and combined) and the ipilimumab treatment arms

Table 34. Time to treatment discontinuation for the pembrolizumab 10 mg/kg Q3W treatment arm

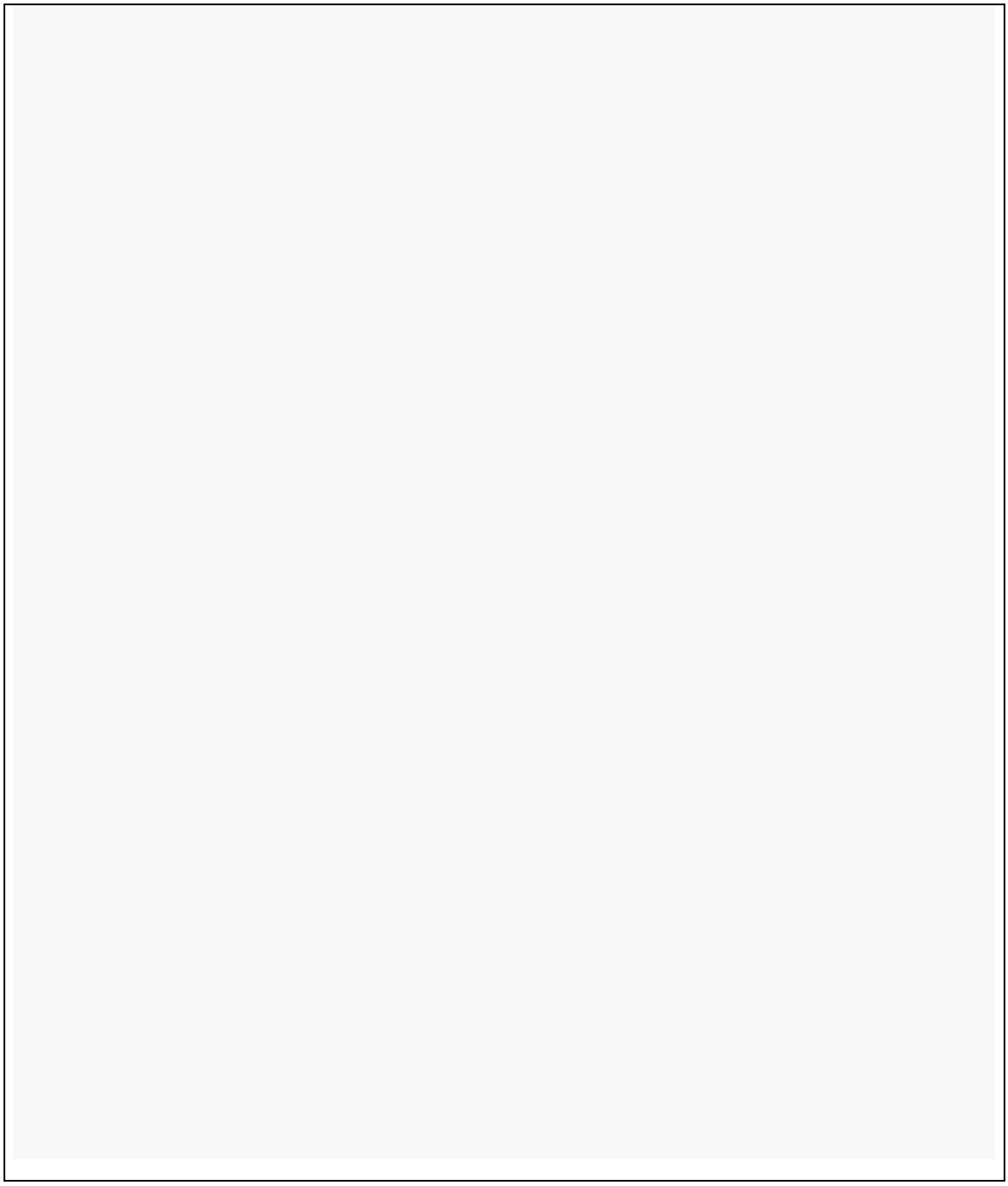


Table 35. Time to treatment discontinuation for the pembrolizumab 10 mg/kg Q2W treatment arm

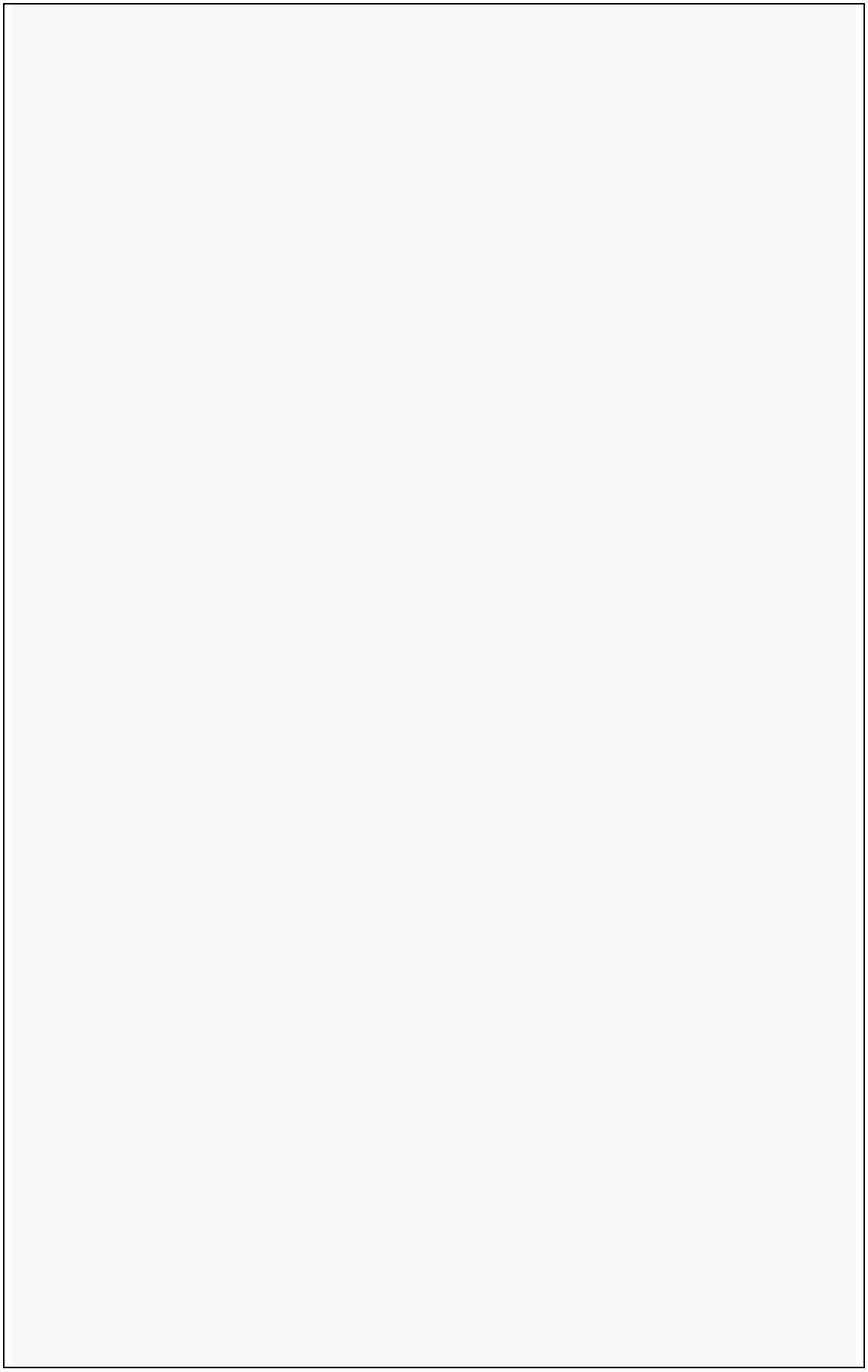
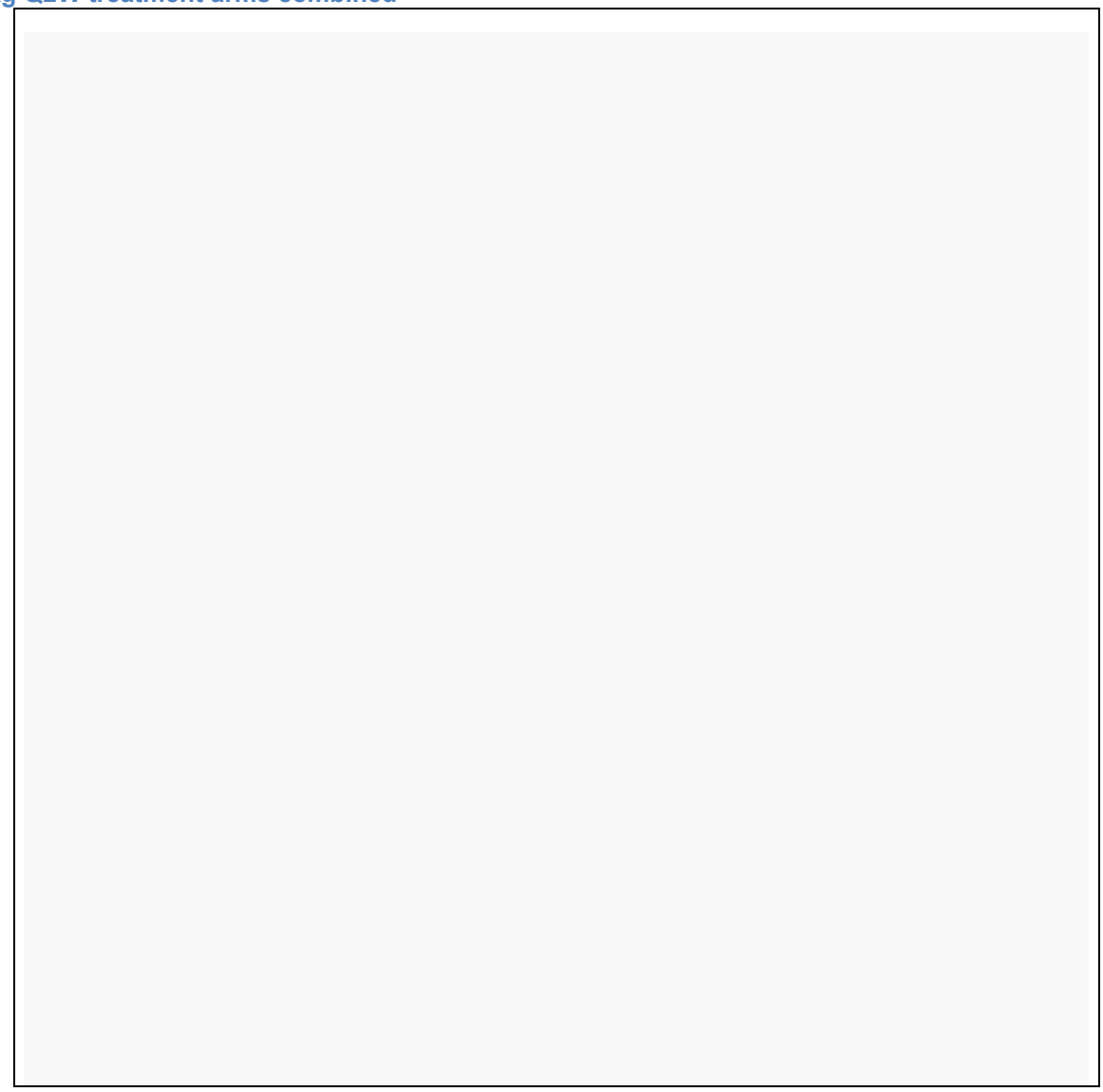


Table 36. Time to treatment discontinuation for the pembrolizumab 10 mg/kg Q3W and 10 mg/kg Q2W treatment arms combined



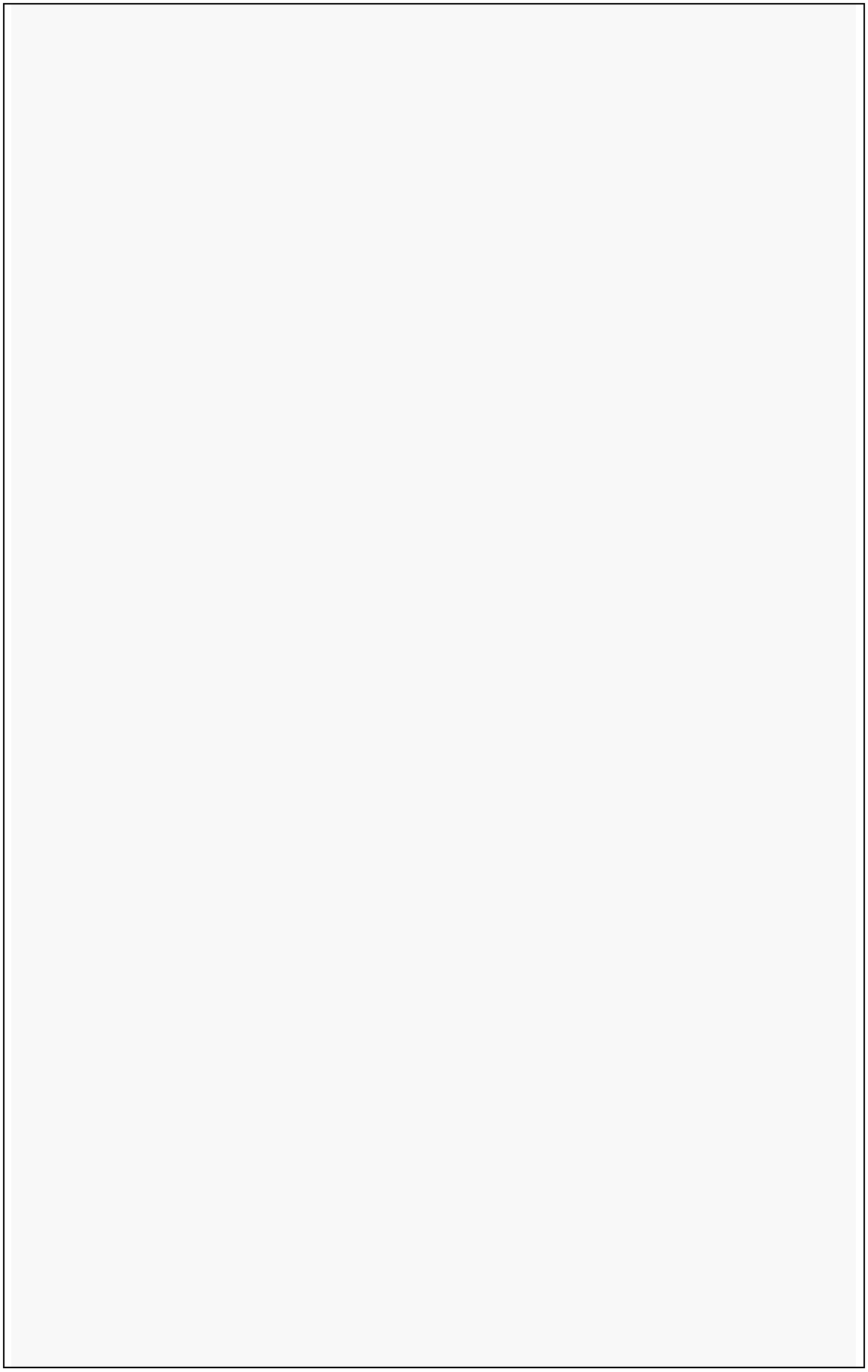
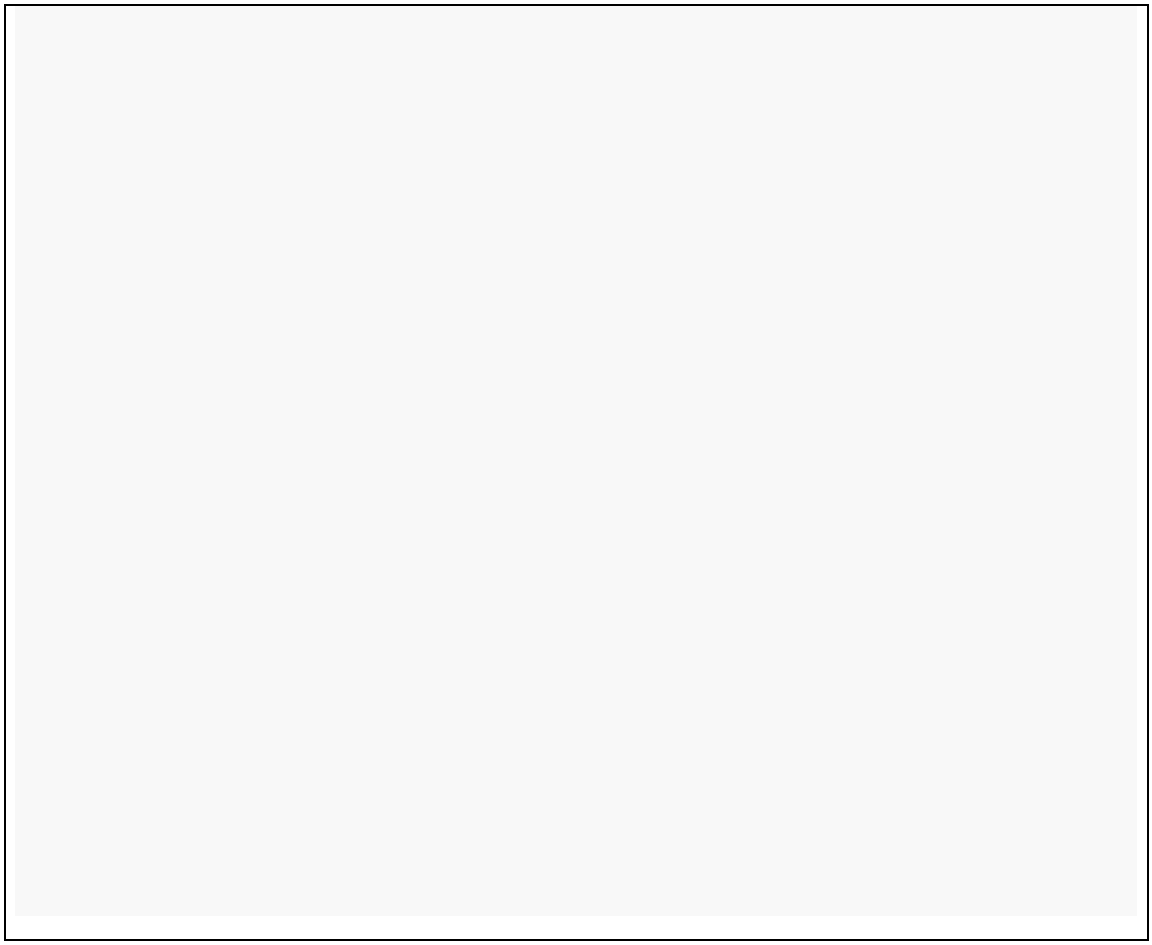


Table 37. Time to treatment discontinuation for the ipilimumab treatment arm



e. Time to progression by investigator assessment (progression-free survival) Kaplan-Meier analysis for patients with BRAFV600 mutation positive disease for both pembrolizumab arms (separately and combined) and the ipilimumab arm, split by those who did / did not receive a BRAF inhibitor prior to commencing the trial (8 analyses).

Patients with BRAF V600 positive mutations: all

Figure 5. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab (10 mg/kg Q3W, 10 mg/kg Q2W and combined) and ipilimumab

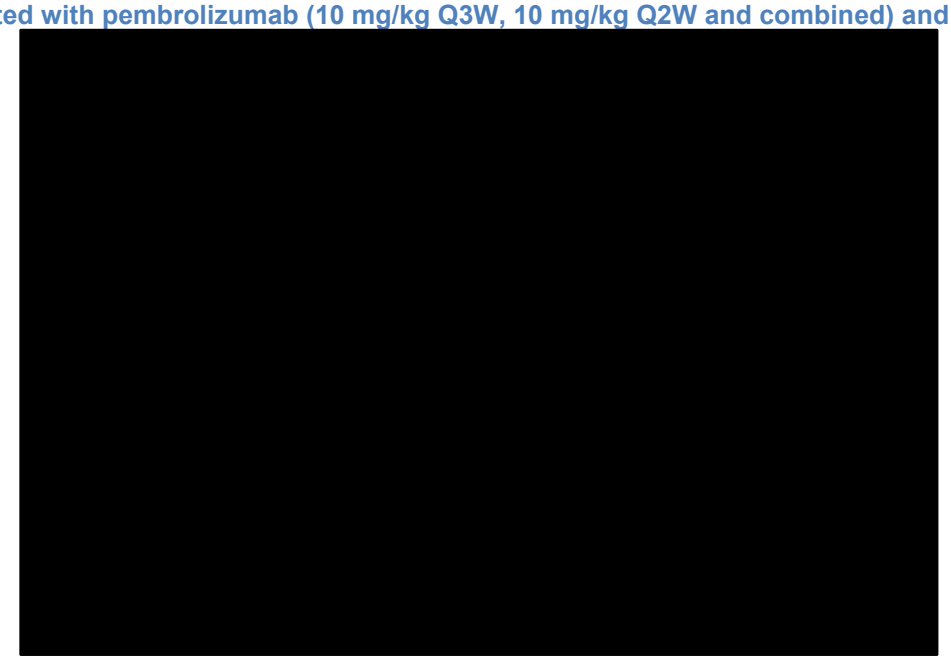


Table 38. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab 10 mg/kg Q3W

Table 39. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab 10 mg/kg Q2W

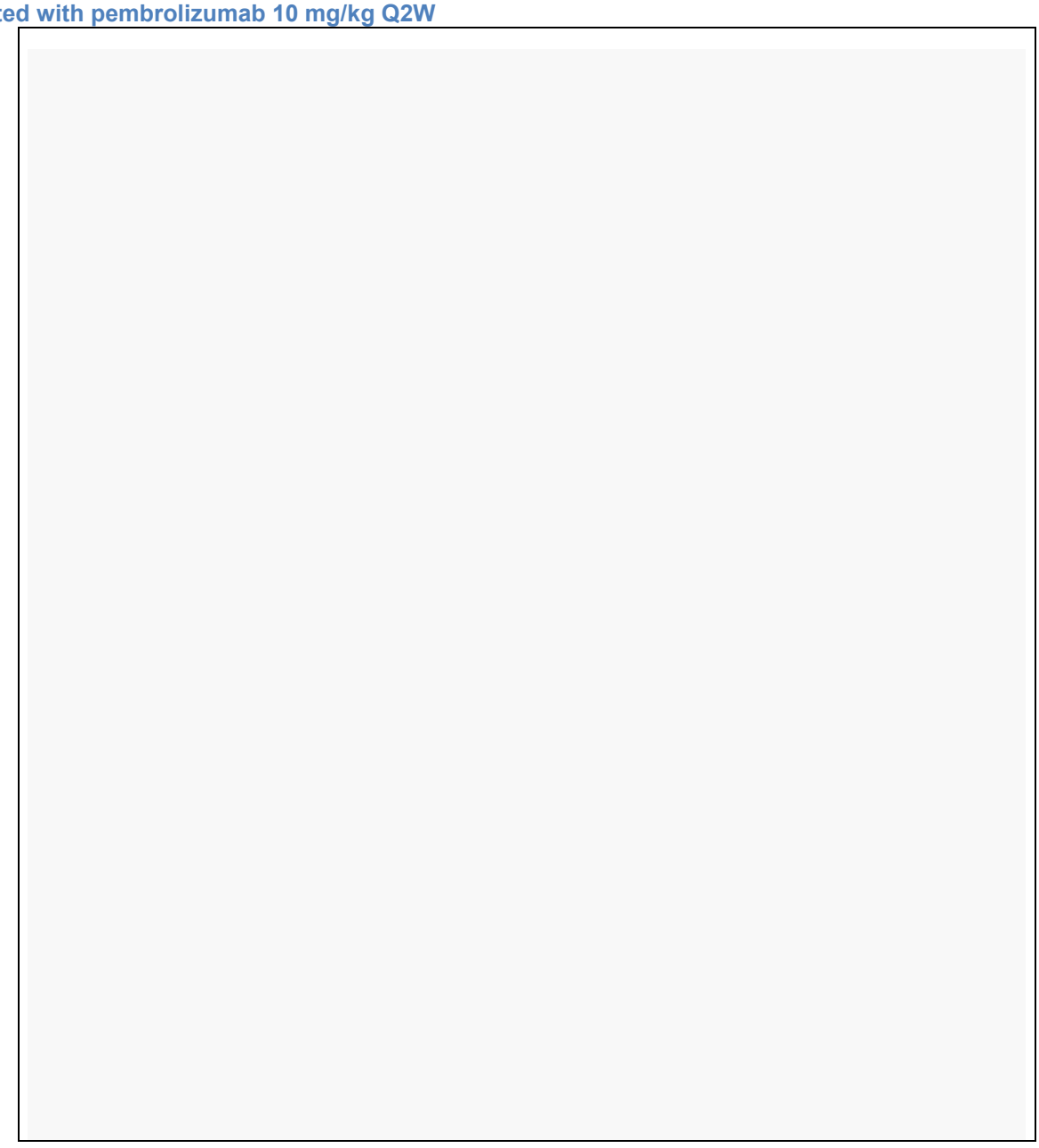
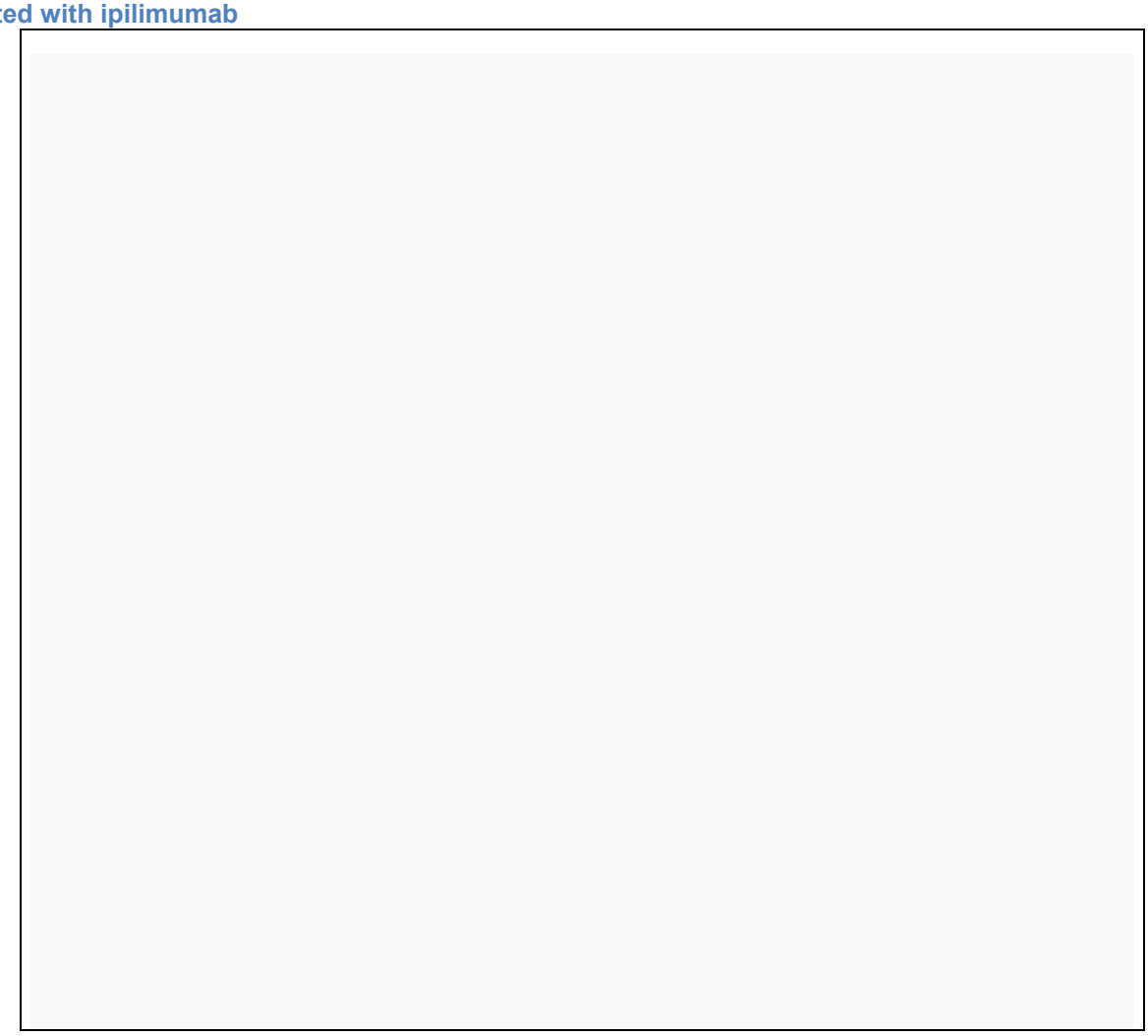


Table 40. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab 10 mg/kg Q3W and 10 mg/kg Q2W combined

Table 41. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with ipilimumab



Patients with BRAF V600 positive mutations who had been previously treated with a BRAF inhibitor

Figure 6. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab (10 mg/kg Q3W, 10 mg/kg Q2W and combined) and ipilimumab who had been previously treated with a BRAF inhibitor

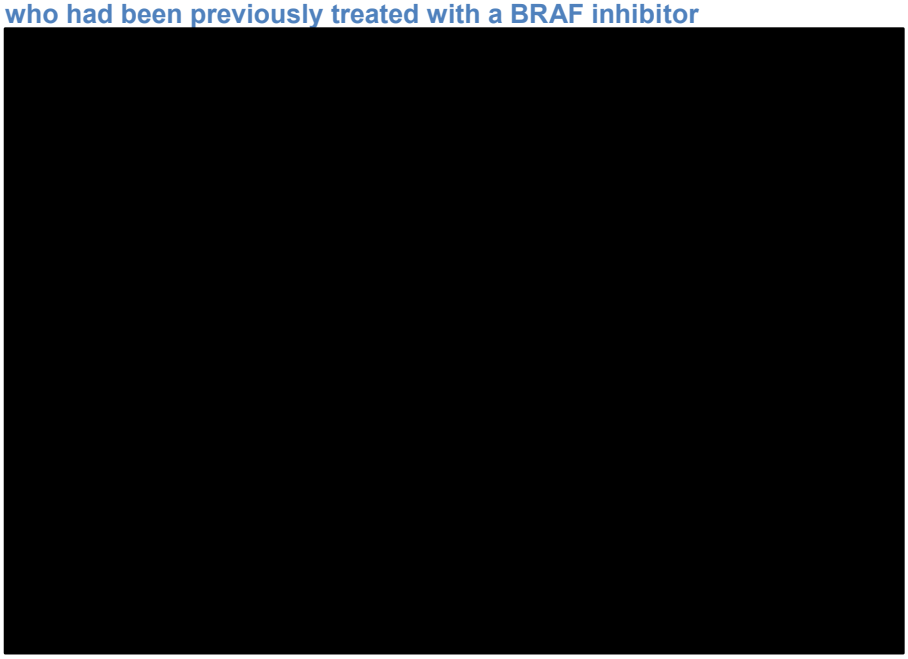


Table 42. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab 10 mg/kg Q3W who had been previously treated with a BRAF inhibitor

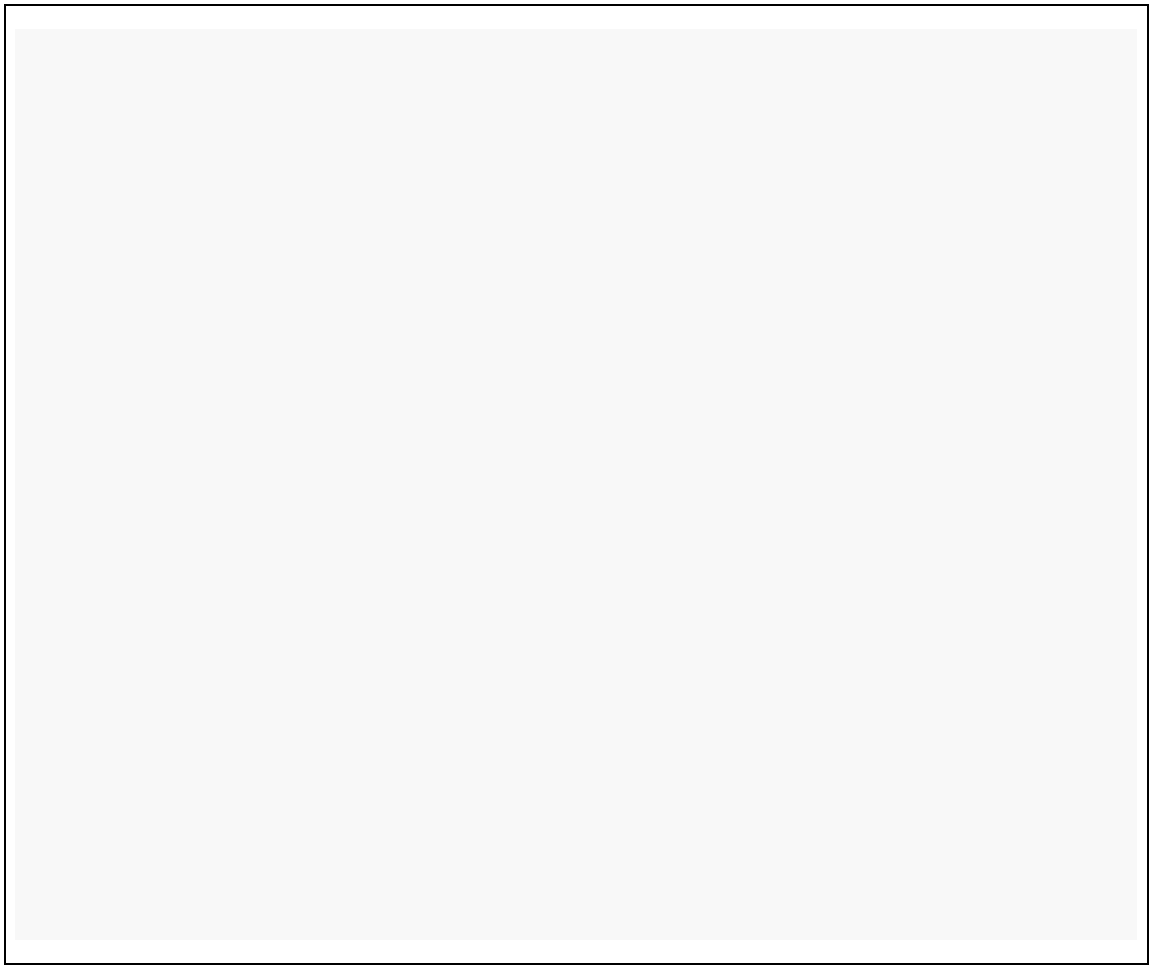


Table 43. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab 10 mg/kg Q2W who had been previously treated with a BRAF inhibitor

Table 44. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab 10 mg/kg Q3W and 10 mg/kg Q2W combined who had been previously treated with a BRAF inhibitor

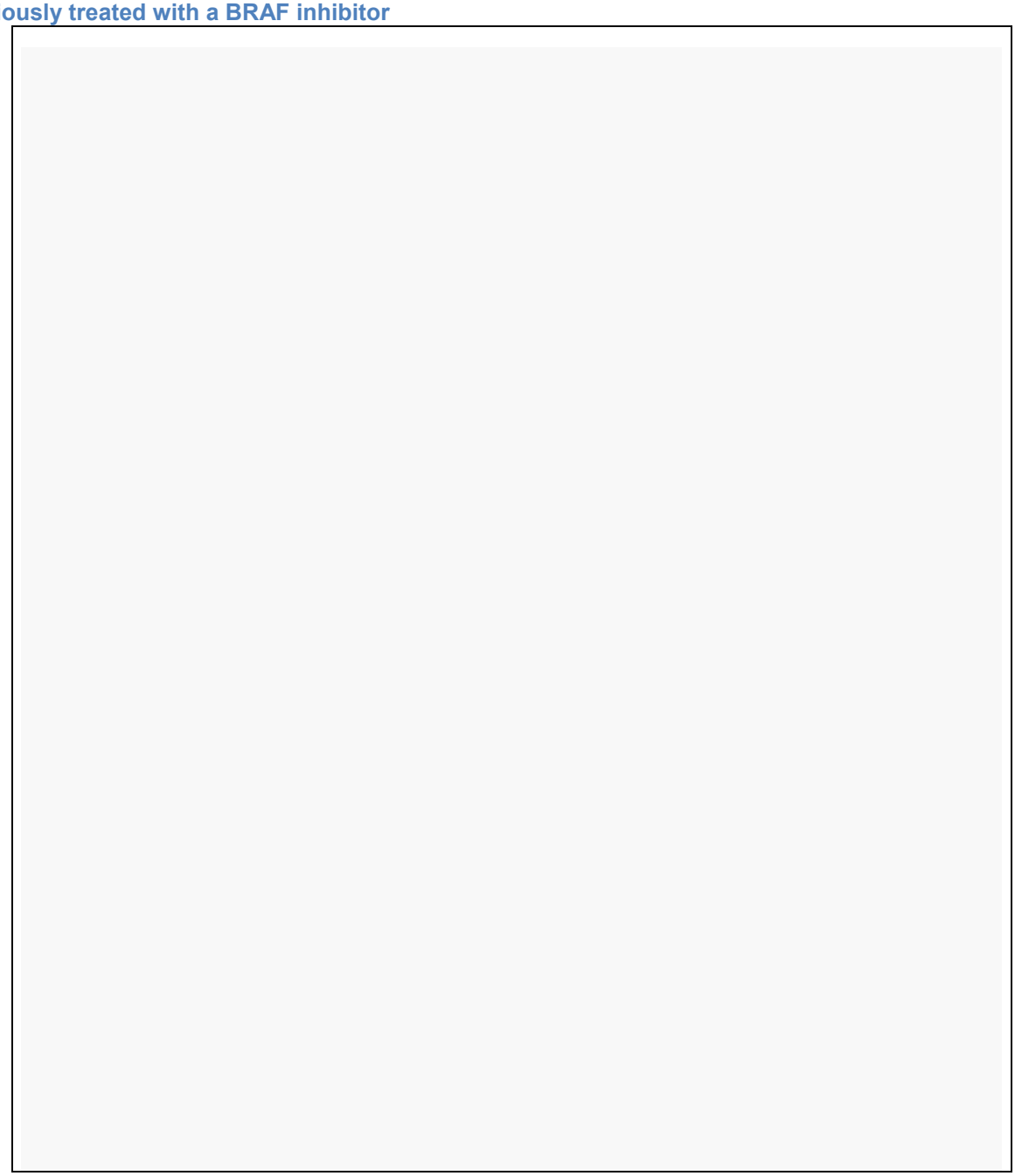


Table 45. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with ipilimumab who had been previously treated with a BRAF inhibitor

Patients with BRAF V600 positive mutations who had not been previously treated with a BRAF inhibitor

Figure 7. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab (10 mg/kg Q3W, 10 mg/kg Q2W and combined) and ipilimumab who had not been previously treated with a BRAF inhibitor

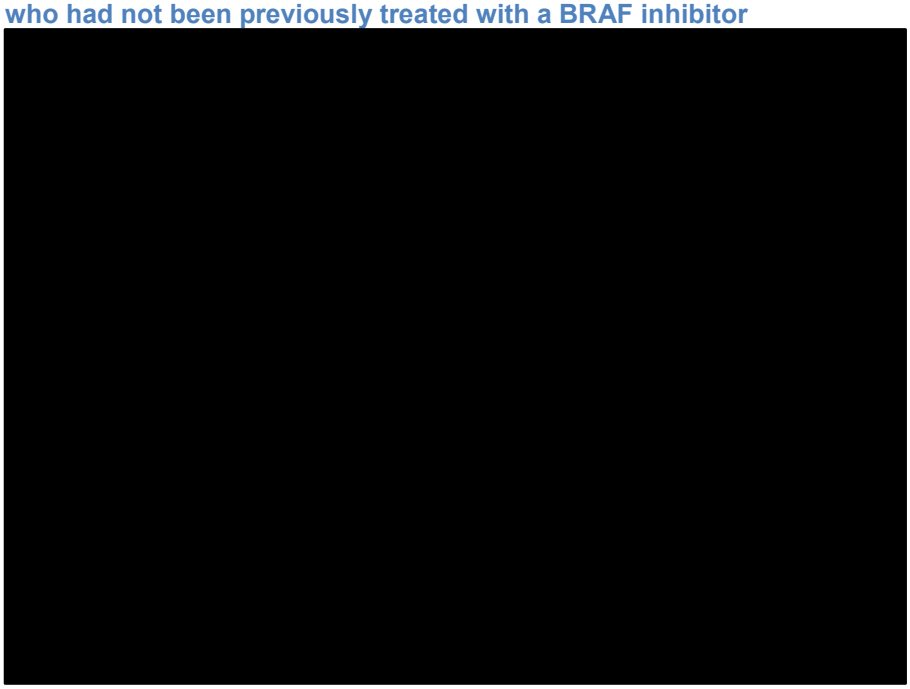


Table 46. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab 10 mg/kg Q3W who had not been previously treated with a BRAF inhibitor

Table 47. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab 10 mg/kg Q2W who had not been previously treated with a BRAF inhibitor

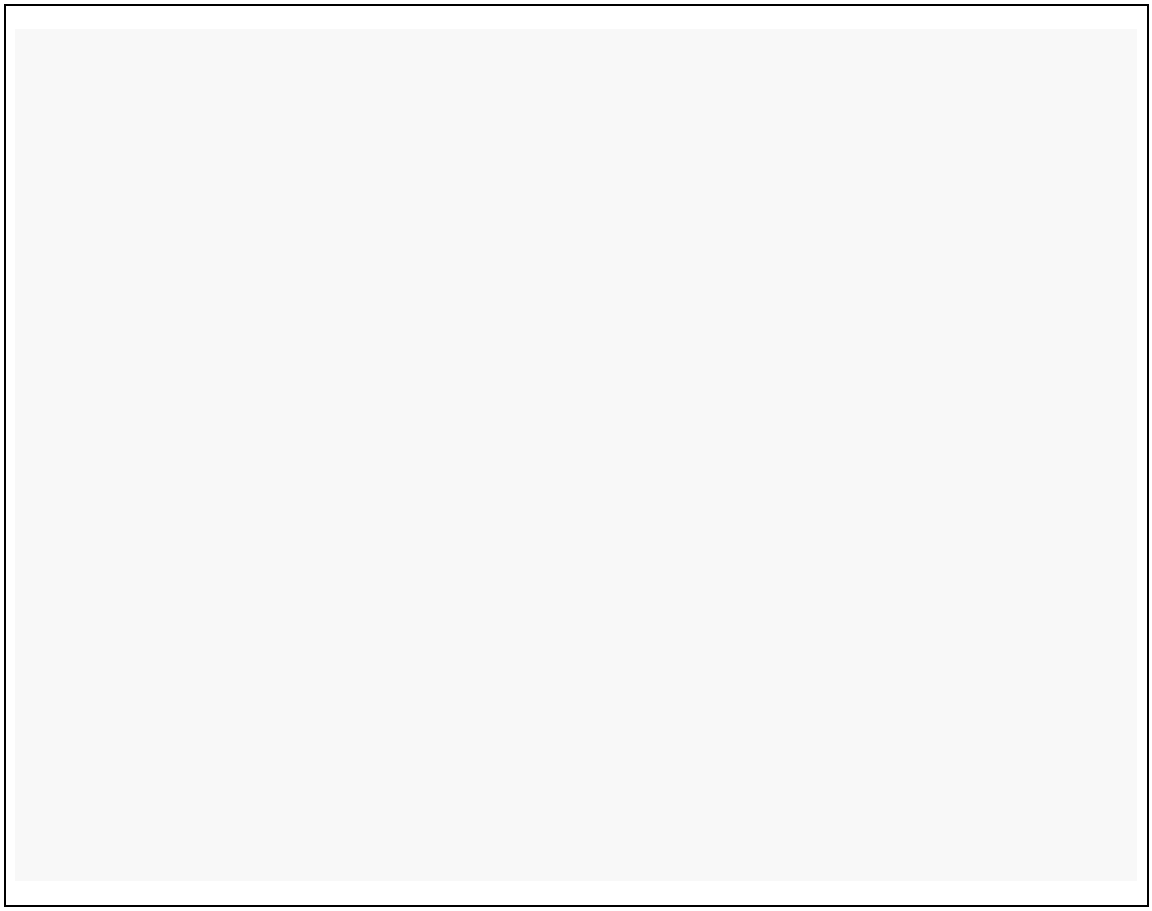


Table 48. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with pembrolizumab 10 mg/kg Q3W and 10 mg/kg Q2W combined who had not been previously treated with a BRAF inhibitor

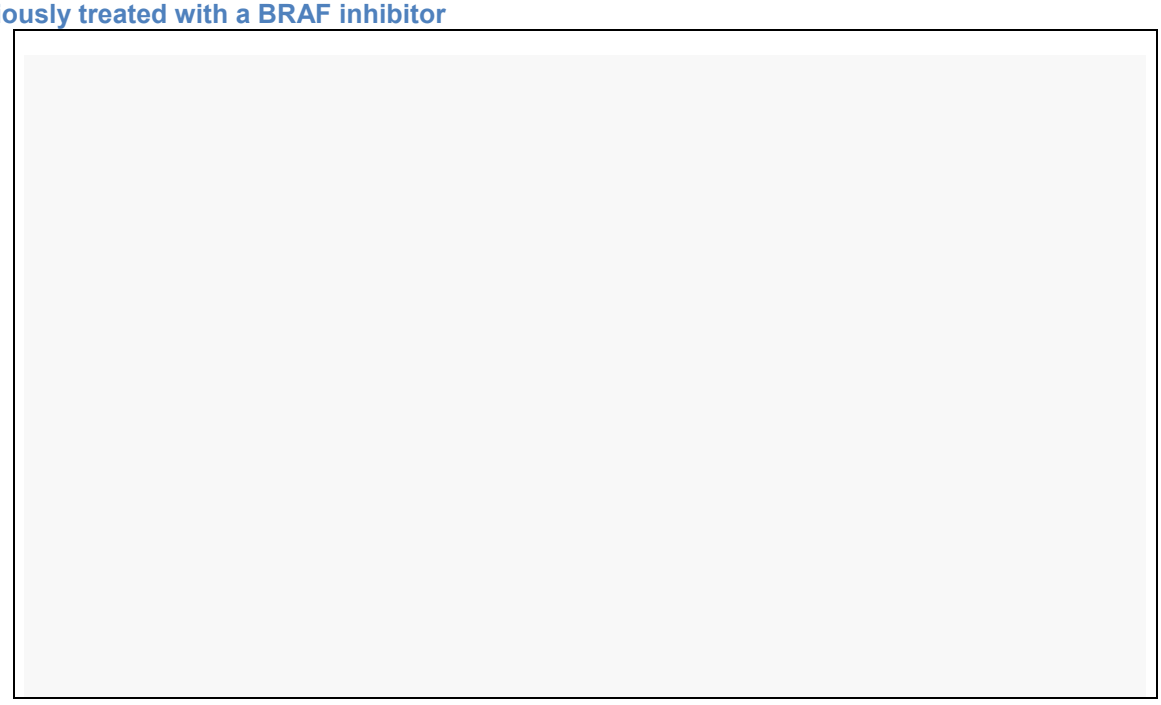


Table 49. KM for PFS (investigator assessment) for BRAFV600 mutation positive patients treated with ipilimumab who had not been previously treated with a BRAF inhibitor

B3. Please provide a table summarising the baseline characteristics as shown in Table 17 of the company submission, together with the time since initial diagnosis of malignant melanoma (mean and range) of patients in the KEYNOTE-006 trial for the three subgroups: 'pembrolizumab treated (both regimens)', 'ipilimumab treated' and 'ipilimumab untreated'.

Table 50. Baseline characteristics for patients in the KEYNOTE-006 trial treated for the pembrolizumab arms combined (both regimens), the ipilimumab treated group and the ipilimumab untreated group

Variable	IPI treated N=256	IPI untreated N=22	Pembro N=556
Median Time since IDMM (range) - day* - No. Missing	650 (27-7618) N=71	722 (63-3885) N=6	752 (36-8534) N=165
Median Age (range) - year	62 (18-88)	62 (18-81)	62 (18-89)
Gender-no.(%)			
- F	109 (42.6)	7 (31.8)	221 (39.7)
- M	147 (57.4)	15 (68.2)	335 (60.3)
Race-no.(%)			
- Missing	0 (0)	0 (0)	3 (0.5)
- ASIAN	4 (1.6)	1 (4.5)	5 (0.9)
- MULTIPLE	1 (0.4)	0 (0)	4 (0.7)
- WHITE	251 (98)	21 (95.5)	544 (97.8)
Region-no.(%)			
- Ex-US	201 (78.5)	13 (59.1)	459 (82.6)
- US	55 (21.5)	9 (40.9)	97 (17.4)
ECOG-no.(%)			
- 0	173 (67.6)	15 (68.2)	385 (69.2)
- 1	83 (32.4)	7 (31.8)	171 (30.8)
LDH level-no.(%)			
- ELEVATED	82 (32)	9 (40.9)	179 (32.2)
- MISSING	6 (2.3)	3 (13.6)	9 (1.6)
- NORMAL	168 (65.6)	10 (45.5)	368 (66.2)
Median baseline tumour burden (range) - mm	55 (10-465)	55 (16-272)	60 (10-554)
Metastasis Stage-no.(%)			
- M0	12 (4.7)	2 (9.1)	18 (3.2)
- M1	5 (2)	0 (0)	10 (1.8)
- M1A	26 (10.2)	4 (18.2)	55 (9.9)
- M1B	50 (19.5)	2 (9.1)	105 (18.9)
- M1C	163 (63.7)	14 (63.6)	368 (66.2)

PD-L1 Status-no.(%)			
- Missing	6 (2.3)	0 (0)	7 (1.3)
- PD-L1 Negative	44 (17.2)	3 (13.6)	103 (18.5)
- PD-L1 Positive	206 (80.5)	19 (86.4)	446 (80.2)
BRAF status-no.(%)			
- MUTANT	97 (37.9)	10 (45.5)	195 (35.1)
- UNDETERMINED	1 (0.4)	0 (0)	6 (1.1)
- WILD TYPE	158 (61.7)	12 (54.5)	355 (63.8)
Brain Metastasis-no.(%)			
- Missing	1 (0.4)	0 (0)	6 (1.1)
- No	228 (89.1)	21 (95.5)	500 (89.9)
- Yes	27 (10.5)	1 (4.5)	50 (9)
Prior line of therapy-no.(%)			
- FIRST LINE	168 (65.6)	13 (59.1)	368 (66.2)
- SECOND LINE	88 (34.4)	9 (40.9)	187 (33.6)
- THIRD LINE	0 (0)	0 (0)	1 (0.2)
Prior Adjuvant/Neoadjuvant-no.(%)			
- No	222 (86.7)	20 (90.9)	484 (87.1)
- Yes	34 (13.3)	2 (9.1)	72 (12.9)
Prior Chemo Therapy-no.(%)			
- No	227 (88.7)	22 (100)	479 (86.2)
- Yes	29 (11.3)	0 (0)	77 (13.8)
Prior Immuno Therapy-no.(%)			
- No	245 (95.7)	21 (95.5)	541 (97.3)
- Yes	11 (4.3)	1 (4.5)	15 (2.7)
Prior systemic BRAF Therapy-no.(%)			
- No	208 (81.2)	14 (63.6)	461 (82.9)
- Yes	48 (18.8)	8 (36.4)	95 (17.1)

B4. Please provide a table showing the baseline age-sex distribution of patients in the KEYNOTE-006 trial in 5 year age bands (under 20 years, 20–24 years, 25–29 years, etc.), for patients in the both pembrolizumab arms jointly and separately, and for the ipilimumab arm.

Table 51: Baseline age-sex distribution for KEYNOTE-006

	Pembrolizumab 10mg Q3W		Pembrolizumab 10mg Q2W		Pembrolizumab combined (10mg Q2W and 10mg Q3W)		Ipilimumab	
Age group	Females	Males	Females	Males	Females	Males	Females	Males
<20	0	0	0	2	0	2	0	2
20-24	1	0	1	0	2	0	1	0
25-29	2	1	3	1	5	2	3	2
30-34	5	7	2	6	7	13	1	4
35-39	3	4	5	7	8	11	4	6
40-44	5	7	6	14	11	21	9	9
45-49	11	8	13	13	24	21	7	13
50-54	13	16	10	13	23	29	14	17
55-59	8	19	16	18	24	37	10	19
60-64	20	22	16	7	36	29	22	23
65-69	17	25	19	22	36	47	20	25
70-74	7	34	14	30	21	64	7	13
75-79	3	19	5	19	8	38	12	13
80-84	8	12	8	9	16	21	6	16

B5. Please provide results for EQ-5D scores in the KEYNOTE-006 trial split between US and non-US patients for the company submission Appendix 30, Table 17, Table 18, Table 20 (but with progression by INV not IRO assessment) and Table 21 (but with progression by INV not IRO assessment).

In light of the ERG request MSD has undertaken further analyses on the EQ-5D scores in the KEYNOTE-006 trial by splitting the results between US and non-US patients for the aforementioned Appendix 30 tables 17, 18, 20 and 21 of the original MSD submission [ID801] but with progression by INV rather than IRO.

Please find below the requested tables (see Table 52, Table 53, Table 54, Table 55, Table 56, Table 57, Table 58, Table 59):

a) Baseline utilities

Table 52: Baseline utilities by treatment group, UK algorithm, US population

	MK3475 10 mg/kg, Q3w					Ipilimumab					Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Baseline	39	39	0.843	0.032	(0.777, 0.908)	43	43	0.806	0.039	(0.727, 0.885)	82	82	0.824	0.026	(0.773, 0.875)

† n=Number of patients with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score

Table 53: Baseline utilities by treatment group, UK algorithm, non-US population

	MK3475 10 mg/kg, Q3w					Ipilimumab					Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Baseline	184	184	0.770	0.018	(0.734, 0.805)	159	159	0.738	0.024	(0.692, 0.785)	343	343	0.755	0.015	(0.726, 0.784)

† n=Number of patients with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score

b) EQ-5D health utility scores analysis by time to death

Table 54: EQ-5D health utility scores analysis by time to death – UK algorithm, US population

Time to Overall Survival (days)	MK3475 10 mg/kg, Q3w					Ipilimumab					Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
≥360*	20	37	0.848	0.033	(0.782, 0.914)	17	38	0.849	0.032	(0.783, 0.914)	37	75	0.848	0.023	(0.803, 0.894)
[270, 360)	1	2	1.000	0.000	NA	2	2	0.780	0.020	(0.526, 1.034)	3	4	0.890	0.064	(0.686, 1.094)
[180, 270)	1	3	1.000	0.000	NA	3	4	0.810	0.085	(0.540, 1.080)	4	7	0.891	0.059	(0.746, 1.037)
[90, 180)	3	6	0.678	0.115	(0.384, 0.973)	4	6	0.485	0.137	(0.134, 0.836)	7	12	0.582	0.090	(0.384, 0.779)
[30, 90)	4	5	0.620	0.149	(0.206, 1.034)	3	3	0.640	0.225	(-0.329, 1.609)	7	8	0.628	0.116	(0.354, 0.901)
<30	1	1	0.080	.	NA	2	2	0.145	0.495	(-6.145, 6.435)	3	3	0.123	0.287	(-1.110, 1.357)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index scores during baseline are not included
* This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days

Table 55: EQ-5D health utility scores analysis by time to death – UK algorithm, non-US population

Time to Overall Survival (days)	MK3475 10 mg/kg, Q3w					Ipilimumab					Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
≥360*	90	182	0.821	0.016	(0.790, 0.853)	59	130	0.788	0.021	(0.747, 0.830)	149	312	0.808	0.013	(0.782, 0.833)
[270, 360)	17	32	0.692	0.057	(0.576, 0.808)	17	28	0.700	0.060	(0.577, 0.823)	34	60	0.696	0.041	(0.614, 0.778)
[180, 270)	34	64	0.623	0.044	(0.535, 0.710)	25	41	0.673	0.044	(0.585, 0.761)	59	105	0.642	0.032	(0.580, 0.705)
[90, 180)	35	61	0.656	0.040	(0.577, 0.736)	34	56	0.673	0.043	(0.587, 0.758)	69	117	0.664	0.029	(0.607, 0.721)
[30, 90)	16	19	0.544	0.074	(0.388, 0.700)	28	46	0.571	0.052	(0.466, 0.676)	44	65	0.563	0.043	(0.478, 0.648)
<30	9	11	0.506	0.140	(0.195, 0.818)	6	6	0.107	0.151	(-0.282, 0.495)	15	17	0.365	0.113	(0.126, 0.604)

† n=Number of patient with non-missing EQ-5D index score

‡ n=Number of records with non-missing EQ-5D index score

EQ-5D index scores during baseline are not included

* This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days

c) EQ-5D health utility score analysis based on progression from KEYNOTE-006 trial (by INV assessment)

Table 56: EQ-5D health utility scores (progression by INV assessment) – UK algorithm, US population

	MK3475 10 mg/kg, Q3w					Ipilimumab					Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	44	146	0.860	0.016	(0.828, 0.892)	42	106	0.824	0.022	(0.781, 0.867)	86	252	0.845	0.013	(0.819, 0.871)
On treatment	44	143	0.860	0.016	(0.827, 0.892)	41	76	0.820	0.027	(0.766, 0.875)	85	219	0.846	0.014	(0.818, 0.874)
Off treatment	2	3	0.873	0.127	(0.328, 1.418)	23	30	0.834	0.034	(0.764, 0.904)	25	33	0.838	0.032	(0.771, 0.904)
Progressive	18	26	0.816	0.041	(0.732, 0.901)	30	36	0.709	0.051	(0.605, 0.813)	48	62	0.754	0.035	(0.684, 0.824)

† n=Number of patients with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline is not included

Table 57: EQ-5D health utility scores (progression by INV assessment) – UK algorithm, non-US population

	MK3475 10 mg/kg, Q3w					Ipilimumab					Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	199	581	0.793	0.009	(0.775, 0.812)	160	398	0.758	0.013	(0.732, 0.783)	359	979	0.779	0.008	(0.764, 0.794)
On treatment	192	561	0.803	0.009	(0.785, 0.821)	155	277	0.750	0.016	(0.718, 0.781)	347	838	0.785	0.008	(0.769, 0.801)
Off treatment	15	20	0.522	0.084	(0.345, 0.698)	80	121	0.776	0.021	(0.734, 0.818)	95	141	0.740	0.023	(0.694, 0.785)
Progressive	100	146	0.682	0.026	(0.630, 0.734)	85	122	0.660	0.031	(0.599, 0.721)	185	268	0.672	0.020	(0.632, 0.711)

† n=Number of patients with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline is not included

d) EQ-5D health utility scores in progression-free state: with and without Grade 3-5 AEs (progression by INV assessment)

Table 58: EQ-5D health utility scores in progression-free state: with and without grade 3-5 AEs (progression by INV assessment), UK algorithm, US population

	MK3475 10 mg/kg, Q3w					Ipilimumab					Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
During Grade3-5 AEs	8	15	0.678	0.078	(0.510, 0.846)	10	20	0.553	0.070	(0.406, 0.699)	18	35	0.606	0.052	(0.500, 0.713)
w/o Grade3-5 AEs	41	132	0.879	0.015	(0.850, 0.908)	38	91	0.863	0.020	(0.824, 0.902)	79	223	0.873	0.012	(0.849, 0.896)

† n=Number of patients with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline is not included

Table 59: EQ-5D health utility scores in progression-free state: with and without grade 3-5 AEs (progression by INV assessment), UK algorithm, non-US population

	MK3475 10 mg/kg, Q3w					Ipilimumab					Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
During Grade3-5 AEs	28	64	0.538	0.038	(0.462, 0.614)	35	76	0.548	0.046	(0.456, 0.639)	63	140	0.543	0.030	(0.484, 0.603)
w/o Grade3-5 AEs	183	531	0.814	0.009	(0.796, 0.832)	145	341	0.788	0.012	(0.765, 0.811)	328	872	0.804	0.007	(0.790, 0.818)

† n=Number of patients with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline is not included

B6. Please provide EQ-5D scores for KEYNOTE-006 as displayed in Table 73 and Table 75 of the company submission for the 10 mg/kg Q2W separately and then combined with the other two pembrolizumab arms. Please clarify why utility values for the patients in the 10 mg/Q2W arm of the trial were not pooled in the initial analysis.

In light of the ERG request MSD has undertaken further analyses on the EQ-5D scores in the KEYNOTE-006 trial by providing the results for tables 73 and 75 of the original MSD submission [ID801] for the 10 mg/kg Q2W separately and then combined with the other two pembrolizumab arms (see Table 60 and Table 62).

Please note that the aforementioned table 73 of the MSD submission [ID801] is relative to IRO assessment while question B5 requested further results relative to INV assessment. As both sets of results (i.e. by IRO assessment and INV assessment) are available we have them provided below for completeness.

Please find below the requested tables (see Table 60, Table 61 and Table 62)

a) Results for table 73 of the original MSD submission [ID801]

a. By IRO assessment

Table 60: EQ-5D health utility score analysis based on progression from KEYNOTE-006 trial (by IRO assessment)

	MK3475 10 mg/kg, Q2W					MK3475 10 mg/kg Q2W + Q3W, Ipilimumab				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	240	738	0.815	0.008	(0.799, 0.831)	672	1879	0.804	0.005	(0.794, 0.814)
On treatment	238	726	0.816	0.008	(0.800, 0.832)	660	1725	0.806	0.005	(0.796, 0.817)
Off treatment	9	12	0.748	0.043	(0.654, 0.841)	106	154	0.778	0.019	(0.741, 0.815)
Progressive	148	255	0.758	0.016	(0.726, 0.790)	420	675	0.720	0.011	(0.698, 0.743)

† n=Number of patients with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline is not included

b. By INV assessment

Table 61: EQ-5D health utility score analysis based on progression from KEYNOTE-006 trial (by INV assessment)

	MK3475 10 mg/kg, Q2W					MK3475 10 mg/kg Q2W + Q3W, Ipilimumab				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	250	791	0.813	0.008	(0.797, 0.829)	695	2022	0.800	0.005	(0.790, 0.810)
On treatment	249	784	0.813	0.008	(0.797, 0.829)	681	1841	0.804	0.005	(0.794, 0.815)
Off treatment	7	7	0.771	0.058	(0.631, 0.912)	127	181	0.759	0.019	(0.721, 0.797)
Progressive	129	202	0.751	0.018	(0.717, 0.786)	362	532	0.712	0.013	(0.686, 0.737)

† n=Number of patients with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score

EQ-5D index score during baseline is not included

b) Results for table 75 of the original MSD submission [ID801]

Table 62: Comparison of utilities reported used in both ipilimumab previously untreated and KEYNOTE-006 economic models

Time to death (days)	MK3475 10 mg/kg, Q2W					MK3475 10 mg/kg Q2W + Q3W, Ipilimumab				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
≥360*	134	285	0.843	0.012	(0.819, 0.866)	320	672	0.827	0.008	(0.811, 0.843)
[270, 360)	21	37	0.692	0.051	(0.589, 0.794)	58	101	0.702	0.031	(0.641, 0.763)
[180, 270)	22	39	0.808	0.031	(0.745, 0.871)	85	151	0.697	0.024	(0.648, 0.745)
[90, 180)	38	65	0.758	0.028	(0.701, 0.814)	114	194	0.690	0.021	(0.649, 0.731)
[30, 90)	30	49	0.593	0.050	(0.493, 0.693)	81	122	0.579	0.031	(0.518, 0.641)
<30	16	17	0.582	0.084	(0.404, 0.760)	34	37	0.445	0.070	(0.302, 0.588)

† n=Number of patient with non-missing EQ-5D index score

‡ n=Number of records with non-missing EQ-5D index score

EQ-5D index scores during baseline are not included

* This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days during this time

The utilities values for the patients in the 10 mg/Q2W arm of the trial were not pooled in the initial analysis as, per the CHMP positive opinion received on May 21st 2015, pembrolizumab licensed dose will be 2mg/kg administered every 3 weeks. For this reason, even though the pembrolizumab doses used in the KEYNOTE-006 clinical trial (i.e. 10mg/kg Q2W and 10mg/kg Q3W) do not reflect the license (i.e. 2mg/kg), we have decided to report the dose that would be administered at the same frequency as the one in the license, meaning every 3 weeks.

Section C: Textual clarifications and additional points

None

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

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: of: [redacted]
NCRI/RCP/ACP
Comments coordinated by [redacted]

Name of your organisation:
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Patients with advanced, inoperable melanoma are normally genotyped for BRAF gene mutation status. The majority of patients with BRAF wild type advanced melanoma will be offered first line ipilimumab, unless it is clear that they have rapidly growing, high volume disease and/or poor performance status and other co-morbidities which might exclude them – in general, it is assumed that patients need to have at least a 3 month life expectancy to stand a chance of benefiting from ipilimumab.
Around 50% of melanomas harbour a BRAF mutation and patients with advanced BRAF mutant melanoma are eligible for BRAF inhibitor treatment as first line therapy (NICE TA 269). However, probably around 2/3 of these patients are now being diagnosed with low volume, slowly progressing disease and these patients who are otherwise fit and well are more likely to be offered immunotherapy with ipilimumab as first line therapy according to NICE guidance (TA 319). Those remaining patients with poorer prognosis advanced melanoma and shorter life expectancy characterized by features including high volume disease, high serum LDH, rapid disease progression, poor performance status and multiple brain metastases will be offered BRAF inhibitors as first line treatment as they are highly unlikely to benefit from ipilimumab.
A very small proportion (<5%) of mainly BRAF wild type advanced melanoma patients may still be offered first line cytotoxic chemotherapy with the aim of debulking disease prior to immunotherapy.

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?

KEYNOTE 006 confirmed that pembrolizumab is more active (statistical significant improvement in all key end points, PFS, OS and response rate) and less toxic compared with Ipilimumab alone. PD1 inhibitors are active in both BRAF mutant and wild-type disease.

There are currently no reliable biomarkers for usefully predicting response to pembrolizumab with enough accuracy to aid clinical decision making..

For patients with braf mutant melanoma, Pembrolizumab provides an additional option to braf directed therapy. There is no clinical reason to exclude patients who have the option of being treated with braf directed therapy from immunotherapies.

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Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

Patients with pre-existing autoimmune disease have been excluded from immune checkpoint inhibitor trials. A small retrospective review of 12 patients reported worsening of symptoms or flare following treatment with ipilimumab (ASCO 2015 poster) which was effectively managed with corticosteroids and tumour responses were recorded.

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)?

Pembrolizumab should be prescribed only by specialist melanoma oncologists in secondary care. In view of immune-related toxicities, there is a need for support from and education and training of acute oncology and acute medical services including A&E teams, gastroenterology, endocrinology, neurology and respiratory medicine. The toxicity profile of pembrolizuamb is significantly more favourable compared with Ipilimumab. Grade 3+ immune-related adverse events are likely to occur in over 10% of treated patients however only a minority of these will require hospitalisation.

In contrast to Ipilimumab which involves up to 4 IV infusions over 12 weeks, pembrolizumab is administered IV every 3 weeks for up to 2 years. This represents a significant burden on chemotherapy delivery units. On the other hand, it is very safe to administer, with allergy reactions virtually unheard of. For this reason, the potential for administration by nurses less highly qualified than chemotherapy day unit nurses should be considered.

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?

Specialist melanoma oncologists can currently access pembrolizumab for patients who have previously received ipilimumab via the Early Access to Medicines Scheme (EAMS). There has been considerable uptake nationally, allowing extensive experience with using the drug. The pembrolizumab European licence is awaited and is anticipated to provide access to both previously treated and previously untreated melanoma patients.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NICE guidelines for melanoma management are due to be published in July 2015 and therefore will predate this technology appraisal

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

See previous discussion regarding need for education and training as well as support from acute medical and oncology services regarding toxicity management.

Although PDL1 tumour expression has been evaluated in trials as a potential predictive biomarker, the studies published to date have not shown compelling evidence that it is has clinical utility.

Treatment should stop if there is severe drug-related toxicity or disease progression. The concept of 'pseudoprogression' described with ipilimumab is probably not as applicable to anti PD-1 inhibitors and there is currently no justification to treat beyond 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?

KEYNOTE 006 was an international randomised trial and recruited at a number of sites in the UK. The trial evaluated 2 pembrolizumab regimens, 10mg/kg administered every 3 weeks and 10 mg/kg administered every 2 weeks, compared with standard ipilimumab. There was no difference between the 2 pembrolizumab arms, and both were superior to ipilimumab for the primary end points, PFS and OS, as well as for secondary end points of response rate. These data represent clinically meaningful incremental benefits for advanced melanoma patients. However, longer term survival is needed to be sure that pembrolizumab offers durable remissions for a subgroup of treated patients who respond, as has now been demonstrated for the subgroup of patients who respond to ipilimumab.

Other pembrolizumab trials have evaluated other dosing regimens and there is insufficient evidence to confirm that dose or administration frequency influences

outcome. If the regimen of 2mg/kg every 3 weeks is confirmed as the licensed regimen, it is reasonable to accept this as an appropriate regimen to substitute for those used in the KEYNOTE 006 trial and adopt in clinical practice.

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 side effect profile of pembrolizumab is favourable compared with Ipilimumab. The KEYNOTE 006 trial reported 10 – 13% grade 3+ AEs occurring in the pembrolizumab arms compared with 20% in the ipilimumab arm. The pattern of immune-related toxicities was not dissimilar, although endocrinology events were more associated with hyper- and hypothyroid with fewer panhypopituitary events associated with pembrolizumab.

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)?

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Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

See above discussion regarding
1) education, training and support of acute oncology and acute medical staff
2) service delivery of this technology

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

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: Dr Martin Highley

Name of your organisation: Melanoma Focus

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.)?
- I am employed by Plymouth Hospitals NHS Trust
- 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?

The current first line treatment options for advanced melanoma in the NHS are a B-RAF inhibitor (vemurafenib or dabrafenib) for patients with a melanoma which harbours the B-RAF^{V600E} mutation; ipilimumab, an immunotherapeutic agent which blocks cytotoxic T-lymphocyte associated protein 4 (CTLA-4); and dacarbazine, a chemotherapeutic agent.

The rate of B-RAF positivity is 50%. Responses to B-RAF inhibition can occur relatively quickly, and B-RAF inhibitors are usually used first line in B-RAF positive patients with disease that is progressing rapidly, when an immediate response is required. However, B-RAF inhibitors usually need to be administered continuously, and associated side effects can have a significant impact on quality of life. B-RAF positive patients with indolent, slowly progressing disease are often treated first line with ipilimumab, but most patients with this mutation will at some point receive a B-RAF inhibitor.

Ipilimumab is most often used in the first line treatment of melanoma, although it is also used as second line treatment in selected patients with B-RAF positive disease following a B-RAF inhibitor. Only four three weekly cycles are administered. Responses to ipilimumab can take some time to develop, occasionally appearing only after completion of treatment, but they can be of long duration. The immune side effects of ipilimumab need monitoring carefully and treating promptly, and may not manifest until after completion of the four cycles.

Dacarbazine is usually used as first line treatment in B-RAF negative patients who are unable to tolerate ipilimumab.

The approach to choosing first line treatment for advanced melanoma is fairly uniform throughout the country, and is guided by recent NICE publications.

The monoclonal antibody pembrolizumab inhibits the programmed cell death 1 (PD-1) immune checkpoint, which is positioned at the effector stage of the immune system. Pembrolizumab has been available in England since 2014, initially via a compassionate use programme, and then between March 2015 and July 2015 through an Early Access to Medicines scheme. It was used in patients who had been treated with ipilimumab and, if B-RAF positive, a B-RAF inhibitor. Pembrolizumab is now licensed as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma.

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Pembrolizumab is administered every three weeks. It is well tolerated and appears to elicit faster responses than ipilimumab, which is an advantage when initiating treatment in patients with progressing disease.

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.

Although the time to response is shorter than that seen with ipilimumab, there are still patients who present with rapidly progressing disease who, if B-RAF positive, are best treated with a B-RAF inhibitor. Melanoma patients also have a high incidence of brain metastases which are difficult to treat. Ipilimumab has been shown to be beneficial in this situation, and one would expect future data to show a similar effect with pembrolizumab.

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)?

Pembrolizumab should only be used in secondary care, under the supervision of an oncologist. Melanoma centres in the UK are already experienced in the routine use of ipilimumab, and education of the acute oncology services has been important in ensuring safety. These arrangements will be sufficient for the safe use of pembrolizumab, which causes less toxicity than ipilimumab.

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?

Pembrolizumab has been available in the UK since 2014, through a compassionate use programme and the Early Access to Medicines scheme.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NICE guidelines for the management of melanoma were published in July 2015.

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?

Pembrolizumab is easily administered as a 30 minute infusion in chemotherapy outpatients. Treatment continues until disease progression or unacceptable toxicity, which will lead to a corresponding increase in the workload of chemotherapy day units.

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.

Pembrolizumab should be available to patients with brain metastases, and those with rarer non-cutaneous advanced melanoma. Experience with pembrolizumab in non-cutaneous melanoma is limited, but ipilimumab has been shown to have some benefit.

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 Keynote-006 study, which included UK centres, was a randomised phase 3 study comparing pembrolizumab 10 mg/kg, every two weeks or every three weeks, and ipilimumab 3 mg/kg for four cycles. No more than one previous systemic therapy for advanced disease was allowed; 65.8% of patients had not received previous systemic therapy.

The first interim analysis, together with overall survival data from the second interim analysis, have recently been published. Both pembrolizumab arms showed an increased 6 month progression free survival (47.3% when given two weekly and 46.4% when given three weekly) compared to ipilimumab (26.5%). The corresponding estimated 12 month survival rates were 74.1%, 68.4% and 58.2%. The response rate was also higher in the pembrolizumab treated patients (33.7% with the two weekly schedule and 32.9% with the three weekly schedule, compared to 11.9% with ipilimumab).

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Single Technology Appraisal (STA)

The median time to response was 86 days (range 32 to 212) in the patients receiving two weekly pembrolizumab, 85 days (range 36 to 251) in those receiving three weekly pembrolizumab, and for those receiving ipilimumab it was 87 days (range 80 to 250).

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?

In the Keynote-006 study, fatigue was the most frequent side effect of pembrolizumab, occurring in 20.9% and 19.1% of patients on the two week and three week schedule respectively. The corresponding figures for diarrhoea were 16.9% and 14.4%. Diarrhoea occurred at grade 3 or 4 severity in 2.5% and 1.1% of patients receiving two weekly and three weekly pembrolizumab respectively, with other grade 3 or 4 reactions reported in fewer than 1% of patients. In patients receiving ipilimumab, the most common toxic effects were pruritus (25.4%), diarrhoea (22.7%), and fatigue (15.2%). Grade 3 and 4 reactions were seen in less than 1% of patients apart from diarrhoea (3.1%) and fatigue (1.2%).

Thyroid dysfunction was described more commonly in patients receiving pembrolizumab, whilst those receiving ipilimumab experienced more colitis and hypophysitis. The need to permanently stop treatment as a result of adverse reactions was lower in the pembrolizumab treated patients (4.0% and 6.9% compared to 9.4% in those receiving ipilimumab), and the only treatment related death occurred in the ipilimumab arm.

Approximately 10% of patients receiving ipilimumab in routine clinical practice require hospitalisation for immune related toxicity. A small number of treatment related deaths have occurred following ipilimumab, but to date none have been reported after pembrolizumab. My personal experience has been that pembrolizumab is less toxic than ipilimumab. Patients often become fatigued, and thyroid dysfunction has developed, which is easily managed. I have not seen the colitis, uveitis, hypophysitis, and skin rash which I have seen with ipilimumab.

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;

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

- 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

N/A

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

N/A

Implementation issues

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)?

NHS staff routinely administer ipilimumab, and no further training will be needed to give pembrolizumab. Ipilimumab is given as a 90 minute infusion every three weeks, although there is evidence that the infusion time can be reduced. Pembrolizumab infusions are shorter (30 minutes), potentially resulting in a time saving in chemotherapy day units. However, pembrolizumab is given three weekly until

disease progression or unacceptable toxicity, compared to the four three weekly cycles of ipilimumab, so this will increase the work load in pharmacies and chemotherapy day units.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided **NCRI/RCP/ACP** and consequently I will not be submitting a personal statement.

Name: .....Dr Pippa Corrie

.....

Signed: .....

.....

Date: 18 08 15

.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. *About you*

Your name: Gillian Nuttall
Name of your nominating organisation: Melanoma UK
Do you know if your nominating organisation has submitted a statement?

☐ ☐ **No**

Do you wish to agree with your nominating organisation's statement?

☐ ☐ None submitted

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☐ **No**

- a carer of a patient with the condition?

☐ Yes ☐ **No**

- a patient organisation employee or volunteer?
-

☐ **Yes** ☐ No

Do you have experience of the treatment being appraised?

☐ ☐ **No**

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. *Living with the condition*

What is your experience of living with the condition as a patient or carer?

Advanced Melanoma is a brutal disease and a patient living with the disease *without treatment* can expect to survive between 3-9 months without treatment. The disease disproportionally affects young people and in an advanced stage, this can mean a young patient is looking at a very limited life expectancy and all the trauma that that brings.

3. *Current practice in treating the condition*

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Treatment in advanced melanoma has always been a complicated area of medicine. Up until the last few years, advanced melanoma was notoriously difficult to treat and clinicians had limited treatment options. The treatment being appraised today has been seen as a step change in the treatment of advanced patients. Patients have reported reduction in tumours and minimal side effects. The side effects of some treatments are debilitating and this is a very important issue for patients and carers.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

As a patient advocacy group we are aware of other treatments in advanced melanoma. Not all of them are appropriate or suitable for all patients and each treatment has its own advantages and disadvantages. Given that we only have anecdotal evidence from patients as to the efficacy of these treatments, it is really for the patient expert to advise on acceptability.

4. *What do you consider to be the advantages of the treatment being appraised?*

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms

- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Improved prospect of quality, long term survival. Evidence of improved patient outcomes and experience to Melanoma UK's knowledge.

Patients have been made aware of instances of better progression free survival which is being seen compared to other treatments and standard of care.

There is the potential to see great overall survival data but we understand that data is still being collected due to cross over in trials.

There are fewer reported side effects than the current standard of care.

This treatment is administered three weekly which patients will find easier to cope with than other regimens.

Targets an area of high unmet need. Melanoma is on the increase in the UK and leading clinicians have made it clear that there is a desire to be able to offer as many alternative treatments as possible as early as possible in the treatment pathway. This is not just limited to clinicians – patients and carers have a strong appetite to have access to as many treatments as possible.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

As mentioned previously. It is reported that this treatment has less side effects and certainly is more tolerable than some other treatments currently available.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

From the information currently available to patients, the only disadvantage to this treatment could be side effects that some patients might be unable to tolerate, although fewer are reported. Also, as with other treatments it may not work in some patients who will see progression of disease. It is also worth noting that patients who have not been previously treated with Ipiliumab might be in a better condition health wise, than if they had. Many patients have reported a lot of significant side effects with Ipi meaning that they might be in a worse starting position than if they are Ipi naïve.

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. *Patient population*

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. *Research evidence on patient or carer views of the treatment*

Are you familiar with the published research literature for the treatment?

☐ Yes ☐ **No**

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

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?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. *Equality*

NICE is committed to promoting equality of opportunity and eliminating

discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Better progression free survival and fewer side effects

Is there anything else 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.

- Meets the need of advanced melanoma patients
- Fewer side effects
- The opportunity to have this treatment without having to "fail" another.
- Giving another option for patients and clinicians
-

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Kathryn Silvester-Eccles
Name of your nominating organisation: Melanoma UK
Do you know if your nominating organisation has submitted a statement?

x No

Do you wish to agree with your nominating organisation's statement?

x N/A

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

x Yes

- a carer of a patient with the condition?

x Yes

- a patient organisation employee or volunteer?
-

x No

Do you have experience of the treatment being appraised?

x Yes

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I am a patient that has lived with metastatic melanoma since 2010. I originally had a 0.9mm mole on the upper left leg removed having noticed that it had altered slightly. I was informed following this removal that the mole had returned a pathology of malignant melanoma. Following this the next procedure was to carry out a wide local excision. This was completed with clear margins and so routine checks ensued at the local hospital.

In December 2012 I noticed a lump in my left groin. After a couple of weeks I raised this with the nurse at the hospital as it had not gone down. I was sent for a needle biopsy but this was clear. AT MDT it was decided to remove the lump. This surgery took place in February 2013 and was declared positive for melanoma. I had an inguinal lymph node removal in late March and 5 nodes were found to be positive for melanoma.

As a result of this diagnosis and my local hospital offering little treatment options I asked for a second opinion at Southampton hospital. As a result of this I started a trial involving dabrafenib in combination with tramatenib. This was a year long program of treatment. At the end of this program I was classed as nil evidence of disease.

In December 2014 a scan showed that the melanoma had spread through the lymphatic system within the pelvis, right groin, abdomen and back. I had treatment with IPI. After two treatments the side effects from this treatment were not manageable and also a scan showed further progression.

I started Pembro on 5th March 2015 and to date have received 7 doses.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Currently there is no known cure for metastatic melanoma that cannot be operated on. As a patient the ultimate hope would be for a cure for this condition. It is understood that at present the data and information from pembro offers shrinkage in the tumours within responding patients and therefore a prolonged lifespan and quality of life.

For me this is my aim is to have as long as possible without the disease affecting my quality of life.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

In my experience there was little the local oncology centre would offer for advanced melanoma. I chose to attend a centre of excellence in order to be proactive about my treatment and options. This poses logistical issues with travel time and energy expenditure to this centre.

I have only one treatment option at present. If I had to compare it to other treatments an oral treatment would always be preferable however there is an acceptance that an infusion is my only option. The treatment s every three weeks and this is not too intensive nor does this adversely impact on my life plans to attend clinic for this treatment plan.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)

- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Melanoma progression being slowed or reversed.

Pain from tumours being reduced

Quality of life improvement

Physical symptoms

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Proven effect on patients in reducing tumours and therefore significant improving the quality of life of these patients and their families.

Although there are side effects for some patients these are not as apparent and frequent as with other drugs such as IPI. Therefore the benefits the treatment can offer without the significant impact on quality of life is a real improvement on what is available.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I am not aware of any differences of opinion

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might

be willing to accept or tolerate and which would be difficult to accept or tolerate)

- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

I am not sure I have concerns overall, however not having pembro available as a first line treatment when it appears to be more beneficial than current options would be my current concern. I appreciate there is a cycle to all new treatments however there is a clear benefit to this treatment above any other available at the moment. In addition although there are side effects the majority of these are manageable without too much impact on activities of daily living.

In addition it would be beneficial for patients and Consultants to have a treatment choice.

Please list any concerns you have about the treatment being appraised.

I cannot think of any aspects the treatment cannot help with at this time. For me it has had a real physical and mental health benefit.

The treatment is infusion rather than table and so does require hospital attendance. This however is only every three weeks and therefore does not impact significantly on other activities. It is also worth noting that the infusion is short and therefore extended treatment sessions are avoided.

I have experienced side effects on this treatment, however these have been less than those on previous treatment regimes. These include fatigue, palpitations, hand tremors, night sweats, joint pain and occasional upset bowel motions. The majority of these have been short lived or come and go. The main long term side effects have been fatigue and joint / muscle pain. This has continued through from the IPI and not really let up – I am therefore not able to say this is completely linked to pembro.

The side effects I accept as a given for the potential benefits the pembro may give. Despite the side effects I am still able to work in a full time capacity with some allowance from my employer in flexible working.

The fact there is a treatment option available gives family and friends help and hope for the future. The positivity this can bring to a situation cannot be underestimated. From my personal experience this far outweighs the side effects and also can allow family some sense of routine and belonging to the situation.

The financial impact of the treatment being in Southampton is a considered one. I could opt to alter my treatment centre however I am comfortable and happy with the centre I attend.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Not that I am aware of.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

All patients that qualify for the treatment and are responders. It would appear that with the successes this treatment has had this should be considered a first line treatment over first generation drugs such as IPI. IPI appears to have a lower success rate with greater side effects.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Those where other less invasive options are available and considered to working.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

x Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

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?

x No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

This is a second generation immunotherapy drug that has shown a greater success than previous. It is for all encompassing rather than other drugs that are specific to BRAF status. This drug has less side effects than previous and that is a real advantage in maintaining the patients quality of life.

Is there anything else that you would like the Appraisal Committee to consider?

How important and life changing this drug is for so many patients suffering with melanoma. This is the first real time that a drug has been available that could significantly improve the outcome and quality of life for a significant part of the patient group.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Pembro has a much greater and proven success rate than other drugs before.
- The side effects can be managed with input from the oncology team and from my perspective they are managed well enough for me to continue working full time with a good quality of life
- Although invasive the regime is not overwhelming and allows for patients to function and have a quality of life around hospital visits.
- As above although invasive this does not impact on things like eating and other aspects of daily living as some of the other treatments available.

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab

ID 801

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/177/06

Completed 29 July 2015

CONTAINS CIC information

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab

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Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence, supervised production of the final report
James Mahon	Lead economist, critique of the economic model
Marty Richardson	Critical appraisal of the statistical evidence
Ashma Krishan	Critical appraisal of the statistical evidence
Rabeea'h W Aslam	Critical appraisal of the clinical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence
Angela Boland	Critical appraisal of the clinical and economic evidence
Angela Stainthorpe	Critical appraisal of the economic evidence and critique of the economic model
Adrian Bagust	Critical appraisal of the economic model
Eleanor Kotas	Cross checking of the submission search strategy
Lindsay Banks	Critical appraisal of the company submission
Miranda Payne	Clinical advice and critical appraisal of the clinical sections of the company submission

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

Table of contents

Abbreviations

AE	adverse event
AEOSI	adverse event of special interest
AJCC	American Joint Committee on Cancer
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BSC	best supportive care
CEAC	cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CS	company submission
CSR	clinical study report
DMC	data monitoring committee
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC-QLQC30	European Organisation for Research and Treatment Cancer Quality of Life Questionnaire
EQ-5D	European Quality of Life-5 Dimensions questionnaire
ERG	Evidence Review Group
HRQoL	health-related quality of life
IA1	first interim analysis
IA2	second interim analysis
ICER	incremental cost effectiveness ratio
INV	local investigator assessment
irRC	immune-related response criteria
IPCW	inverse probability censored weighting
IRO	integrated radiology and oncology analysis (central assessment)
ITC	indirect treatment comparison
ITT	intention-to-treat
IVRS	interactive voice recognition system
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
MEK	mitogen-activated protein kinase
MHRA	Medicines and Healthcare Products Regulatory
ORR	overall response rate
OS	overall survival
PD	progressed disease
PD-1	programmed cell death
PD-L1	programmed cell death 1 ligand
PFS	progression-free survival
PPS	post-progression survival
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
Q2W	every 2 weeks
Q3W	every 3 weeks
QALY	quality adjusted life year
RCT	randomised controlled trial
RPSFT	rank-preserving structural failure time
SAE	serious adverse event
SAP	statistical analysis plan

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Merck Sharp & Dohme has submitted clinical and economic evidence to NICE in support of the use of pembrolizumab (Keytruda) for the treatment of advanced melanoma previously untreated with ipilimumab.

1.2 Critique of the decision problem in the company submission

Pembrolizumab is not currently licensed for use in patients with advanced melanoma in Europe. However, in May 2015, the company received a positive opinion from the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) stating that pembrolizumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. The company is expected to receive a European licence for pembrolizumab in July 2015.

The NICE scope and the company's decision problem for this appraisal address only a subgroup of the population covered by the anticipated licence for pembrolizumab, namely patients with advanced melanoma previously untreated with ipilimumab. A second subpopulation, patients with advanced melanoma who have received treatment with ipilimumab, is being addressed in a separate STA appraisal. Pembrolizumab can be used to treat both a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations and those with $BRAF^{V600}$ positive mutations.

The anticipated pembrolizumab licence is expected to be for a dose of 2mg/kg administered every 3 weeks (Q3W). However, in the pivotal trial (KEYNOTE-006) discussed in the company submission (CS), patients were treated with pembrolizumab at a dose of 10mg/kg Q3W (or 10mg/kg every 2 weeks [Q2W]). There is no direct evidence that allows a comparison of the clinical effectiveness of the 2mg/kg Q3W and the 10mg/kg Q3W doses in patients previously untreated with ipilimumab. The draft European Public Assessment Report (EPAR) issued by the CHMP states that the CHMP has accepted that no differences in the efficacy of 2mg/kg and 10mg/kg are to be expected. The ERG cautiously accepts that the 2mg/kg Q3W and 10mg/kg Q3W doses of pembrolizumab are clinically equivalent when used to treat advanced melanoma in a patient population not previously treated with ipilimumab.

The comparators identified in the NICE scope are ipilimumab, vemurafenib, dabrafenib and dacarbazine. The company has used direct evidence from the KEYNOTE-006 trial to support the clinical effectiveness of pembrolizumab versus ipilimumab. The company has used indirect evidence, generated by conducting a series of network meta-analyses (NMAs), to compare the efficacy of pembrolizumab with all of the comparators specified in the NICE scope. Although included as a comparator in the NMAs, the company does not consider dacarbazine to be a relevant comparator to pembrolizumab; the ERG agrees with this approach.

Clinical evidence is reported in the CS for all five outcomes specified in the NICE scope: overall survival (OS), progression-free survival (PFS), response rate (reported as overall response rate [ORR] and disease control rate), adverse events (AEs) of treatment and health-related quality of life (HRQoL). The ERG notes that the KEYNOTE-006 trial was stopped early for benefit at the second interim analysis (IA2) on the recommendation of the Data Monitoring Committee (DMC) and the data currently available from the trial are immature. EuroQol (EQ-5D) data and EORTC-QLQ-C30 data were collected during the KEYNOTE-006 trial. However, the findings are not reported in the clinical effectiveness section of the CS, even though they were used in the base case cost effectiveness analysis.

The economic analyses addressed by the decision problem match those specified in the NICE scope.

1.3 Summary of clinical effectiveness evidence submitted by the company

Direct evidence

The company carried out a systematic search of the literature and identified one randomised controlled trial (RCT), KEYNOTE-006, which compares pembrolizumab (10mg/kg Q3W) with a relevant comparator (ipilimumab). A dose-escalating RCT, KEYNOTE-001 (Part D) and a non-randomised study (KEYNOTE-001 [Part B1]) were additionally identified as providing supportive evidence for the clinical effectiveness of the anticipated licensed dose (2mg/kg Q3W) of pembrolizumab. .

The KEYNOTE-006 trial included patients with $BRAF^{V600}$ wild-type mutations and those with $BRAF^{V600}$ positive mutations. None of the 834 patients in the trial had been previously treated with ipilimumab. However, around 30% of patients had received at least one line of prior systemic therapy.

Data for PFS were available from the 6-month interim analysis (IA1) as measured by central assessment using the Response Evaluation Criteria in Solid Tumours 1.1 criteria. The data indicate a significant effect of pembrolizumab 10mg/kg Q3W in comparison to ipilimumab (HR=0.58; 95% CI 0.47 to 0.72, p<0.0001). The difference in median PFS between the treatment arms also indicates an important treatment effect for pembrolizumab 10mg/kg Q3W versus ipilimumab (4.1 months versus 2.8 months). The efficacy of pembrolizumab was found to be consistent across all subgroups for PFS; no statistically significant p-values for interaction were observed, with the exception of the subgroup analysis by line of therapy.

At 12 months follow-up, the results of IA2 demonstrated a significant treatment effect for pembrolizumab 10mg/kg Q3W compared with ipilimumab (HR=0.69; 95% CI 0.52 to 0.90, p=0.0036). Median OS times were not available at IA2. The OS rates at 12 months were 68.4% for the pembrolizumab 10mg/kg Q3W arm and 58.2% for the ipilimumab arm. No statistically significant p-values for interaction were observed for the other subgroups analyses for OS.

The safety data from the KEYNOTE-006 trial indicate that treatment with pembrolizumab 10mg/kg Q3W was associated with a similar frequency of AEs when compared to treatment with ipilimumab. However, patients treated with pembrolizumab experienced fewer grade 3 to 5 AEs, serious AEs (SAEs), drug-related SAEs and SAEs leading to treatment discontinuation when compared to patients treated with ipilimumab.

Indirect evidence

There is no direct clinical evidence comparing pembrolizumab with vemurafenib or dabrafenib. Hence, the company performed four NMAs using four different scenarios: first-line treatment only (Scenarios 1 and 2) and first- and second-line treatment combined (Scenarios 3a and 3b). To allow the networks to be constructed, the company made a number of clinical and methodological assumptions.

For the first-line population, pembrolizumab was found to statistically significantly improve PFS in comparison to ipilimumab at 3, 6 and 12 months, for all scenarios. There was some evidence that pembrolizumab may improve PFS in comparison to vemurafenib for patients with $BRAF^{V600}$ positive mutations. No statistically significant differences were observed between pembrolizumab and dabrafenib in terms of PFS for patients with $BRAF^{V600}$ positive mutations.

Pembrolizumab was found to statistically significantly improve OS in comparison to ipilimumab at 6 and 12 months, for all scenario analyses. The effect was not statistically

significant at 18 months, with the exception of scenario 3a. No statistically significant differences were observed between pembrolizumab and dabrafenib for patients with $BRAF^{V600}$ positive mutations.

For the second-line population, for OS, no statistically significant differences were observed between pembrolizumab and ipilimumab in terms of OS. Due to lack of available data, second-line treatment for patients with $BRAF^{V600}$ positive mutations was not considered.

The results from these NMAs were **not** used in the company's base case cost effectiveness analyses.

Meta-analyses using data from the KEYNOTE-006 and the KEYNOTE-001 (Part D) trials were not conducted as the company considered that the trial designs and patient characteristics were too different to allow a meaningful comparison.

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For the second-line population, for OS, no statistically significant differences were observed between pembrolizumab and ipilimumab in terms of OS. Due to lack of available data, second-line treatment for patients with $BRAF^{V600}$ positive mutations was not considered.

Meta-analyses using data from the KEYNOTE-006 and the KEYNOTE-001 (Part D) trials were not conducted as the company considered that the trial designs and patient characteristics were too different to allow a meaningful comparison.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG is satisfied with the company's search strategy and stated inclusion/exclusion criteria and is confident that the company did not miss any relevant published papers.

Direct evidence

The ERG considers KEYNOTE-006 to be a well-conducted trial. However, the dose of pembrolizumab given to patients in this trial (10mg/kg Q3W) does not match the anticipated licensed dose (2mg/kg Q3W). The ERG cautiously accepts the EMA's statement that the 2mg/kg Q3W and 10mg/kg Q3W doses of pembrolizumab are clinically equivalent when used to treat advanced melanoma in this patient population.

The ERG is concerned that the KEYNOTE-006 trial was stopped early due to the demonstrated net survival gain of pembrolizumab (10mg/kg Q3W) over ipilimumab at IA2. This means that the available OS data are immature and the true impact on OS may never be fully known. The ERG notes that there is evidence that trials that have been stopped early for benefit have not delivered the anticipated survival gain estimated at the time of stopping.

In the KEYNOTE-006 trial, the original RCT protocol states that treatment with pembrolizumab 10mg/kg Q3W is limited to 24 months. As the trial was stopped early, this stopping rule was never enforced. The ERG is unsure of the consequences of this course of action.

Indirect evidence

In the main body of the CS, the company presents the results of four NMAs using fractional polynomials; these results are not used to inform the company's cost effectiveness base case. The ERG is satisfied that the clinical assumptions made by the company to construct the evidence networks are reasonable. However, the ERG is not confident that the results of the NMAs are valid due to observed methodological weaknesses in this approach.

1.5 Summary of cost effectiveness evidence submitted by the company

To compare the cost effectiveness of pembrolizumab 2mg/kg Q3W with ipilimumab, the company developed a de novo partitioned survival Markov model. The Markov model comprised three health states: pre-progression, post-progression and death. All patients

entered the model in the pre-progression state. Variants of this model structure have been used in the modelling of metastatic oncology for a number of previous NICE STAs. The model has been developed in Microsoft Excel using a 1-week cycle length and the time horizon is set at 30 years. As recommended by NICE, a discount rate of 3.5% has been used for both costs and outcomes; outcomes are measured in quality adjusted life years (QALYs). The model perspective is that of the UK NHS. Survival was estimated based on data from the KEYNOTE-006 trial and published sources. Utility values were calculated from data collected during the KEYNOTE-006 trial. Resource use and costs were estimated based on information from the KEYNOTE-006 trial, published sources and clinical experts. In the company's base case cost effectiveness analysis, costs and benefits were discounted. A Department of Health Patient Access Scheme (PAS) discount was applied to the cost of pembrolizumab and the full list price was used for the comparators.

For the comparison of pembrolizumab 2mg/kg Q3W vs ipilimumab for patients with $BRAF^{V600}$ wild-type mutations, the company's results show that pembrolizumab 2mg/kg Q3W dominates ipilimumab i.e. pembrolizumab 2mg/kg Q3W is cheaper (lifetime costs per patient fall by £21,185) and is also more effective (QALYs increase by 0.44).

For patients with $BRAF^{V600}$ positive mutations, the company's results show that pembrolizumab 2mg/kg Q3W dominates vemurafenib and ipilimumab and has an incremental cost effectiveness ratio (ICER) of £5,852 per QALY gained when compared with dabrafenib.

The company carried out a wide range of deterministic sensitivity analyses. In all of the analyses the two most influential parameters were the shape and the treatment effect of the Gompertz curve used to model PFS for patients receiving pembrolizumab.

The probabilistic sensitivity analysis (PSA) results show that, compared with ipilimumab, for patients with $BRAF^{V600}$ wild-type mutations, the probability of pembrolizumab 2mg/kg Q3W being cost effective at a threshold of £50,000 per QALY gained is approximately 91.6%. The probabilistic ICER for pembrolizumab 2mg/kg Q3W vs ipilimumab, vemurafenib and dabrafenib for patients with $BRAF^{V600}$ positive mutations is 90%.

The company carried out 33 scenario analyses. The only scenarios which resulted in pembrolizumab not being cost effective related to patients with $BRAF^{V600}$ positive mutations and involved using log-normal curves (based on KEYNOTE-006 trial data) to project OS. The company, however, considers these scenarios to be unrealistic as long-term survival for patients receiving ipilimumab was projected below that expected based on published data.

The company considered a wide range of different discounts to the prices of ipilimumab, vemurafenib and dabrafenib and the company's results suggest that, at a willingness to pay threshold of £50,000 per QALY gained, pembrolizumab 2mg/kg Q3W remains the most cost effective treatment in most of the scenarios up to a discount of 60% to the cost of the comparator drugs.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG is satisfied with the company's search strategy and stated inclusion/exclusion criteria and is confident that the company did not miss any relevant published papers.

The ERG has some concerns relating to the overall structure of the company's model due to the fact that pembrolizumab becomes increasingly cost effective the more ineffective it is at preventing disease progression. This is because time in PFS is linked to the cost of pembrolizumab but not to any patient benefit. So, when patients enter the progressive disease state, treatment costs fall but there is no disbenefit in terms of a reduction in quality of life.

Limited data

Limited efficacy data are available. The assessment of cost effectiveness of pembrolizumab vs ipilimumab depends on data from a single phase III clinical trial (KEYNOTE-006) with only 12 months of follow up, which was stopped early for benefit and did not include the anticipated licensed dose of pembrolizumab. The cost effectiveness of pembrolizumab versus the BRAF inhibitors relies on efficacy data for vemurafenib and dabrafenib that have been obtained by digitising published Kaplan-Meier (K-M) curves (for up to 60 weeks). These limited data, in conjunction with data from other published sources, have been used as the basis for projecting survival out to 30 years.

Survival projections

An analysis of the company's base case results shows that 87.5% of the estimated health gain (in terms of additional survival) attributed to treatment with pembrolizumab occurs after 12 months. This means that the method used to project survival is extremely important.

However, in terms of the comparison of pembrolizumab versus ipilimumab, the company's approach to modelling PFS relies on an assumption of proportional hazards. Analysis carried out by the ERG shows that this assumption does not hold. The company's OS projection uses some questionable external data which result in the mortality risk in the second phase of extrapolation being sometimes erratic and occasionally zero.

In terms of vemurafenib and dabrafenib, PFS data are not adjusted for differences in patient characteristics and, whilst OS data have been adjusted, the ERG considers that the method of adjustment employed suffers from a series of limitations that render the results unreliable. Furthermore, for all treatments, the company's approach to projecting OS employs out of date registry data.

Costs

An analysis of the base case results reported in the CS shows that 90.2% of the overall incremental cost saving of pembrolizumab compared to ipilimumab is attributable to differences in direct treatment costs (drug acquisition and administration). Similarly for vemurafenib and dabrafenib the direct treatment costs account for 83.0% and 74.3% of all patient costs (ignoring terminal care costs which are almost identical regardless of the treatment). This means that only variations in the assumed NHS price or length of treatment of pembrolizumab or comparators can have any meaningful effect on the estimated incremental cost per patient between treatments.

Other concerns

The ERG also has concerns relating to how treatment duration was modelled, the dosage calculations and drug administration costs employed in the model.

1.7 ERG commentary on the robustness of evidence submitted by the company

1.7.1 Strengths

Clinical evidence

- The company provided a detailed submission that fulfilled the requirements of NICE's scope. The ERG's requests for further clinical information were fulfilled promptly and to a good standard
- The KEYNOTE-006 trial is considered to be a well-designed and conducted trial that measures efficacy in terms of PFS, OS, AEs and HRQoL, all of which are important outcomes to clinicians and patients.

Cost effectiveness evidence

- Variants of this model structure have been used in the modelling of metastatic oncology for a number of previous NICE STAs
- The decision model submitted by the company is generally implemented correctly.

1.7.2 Weaknesses and areas of uncertainty

Clinical evidence

- There is no phase III RCT evidence to support the use of the anticipated licensed dose of pembrolizumab (2mg/kg Q3W) to treat advanced melanoma in patients

previously untreated with ipilimumab in either a first- or second- line setting. The ERG cautiously accepts the EMA's statement that the 2mg/kg Q3W and 10mg/kg Q3W doses of pembrolizumab are clinically equivalent when used to treat advanced melanoma in this patient population
- The KEYNOTE-006 trial was stopped early for benefit. Whether the anticipated gain from pembrolizumab when compared to ipilimumab will ever be realised is unknown
- The ERG considers the results of the company's NMAs to be unreliable as they appear to be based on flawed methodology.

Cost effectiveness evidence

- For pembrolizumab versus all comparators, the ERG critiques the company's three-phase approach to modelling OS and offers an alternative approach to extrapolation which includes different all-cause age specific mortality rates
- For vemurafenib and dabrafenib, PFS data have not been adjusted for differences in patient characteristics and, whilst OS data have been adjusted, the ERG considers that the method of adjustment employed suffers from a series of limitations that render the results unreliable
- The company uses PFS data based on central assessment for the comparison of pembrolizumab versus ipilimumab. The ERG prefers to use local assessment PFS data as this is more representative of NHS practice
- Where available, rather than use PFS to model treatment duration, the ERG considers that it is more accurate to use time to treatment discontinuation (TTD) data. In addition, the ERG suggests that patient utility should change (values should decrease) on disease progression
- The ERG proposes that the model could be improved by incorporating utility values from a European (non-US) population, calculating dosages based on a UK population weight distribution rather than trial weight distribution and using the same costs for the administration of pembrolizumab and ipilimumab.

1.8 Key issues: summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG implemented six modifications to the company's model:

- An alternative OS extrapolation and non-cancer mortality estimate
- Changing PFS to be based upon local investigator estimates
- Changing treatment duration to be based on time to treatment discontinuation (TTD) rather than PFS
- Combining progressive disease and time to death utilities based on European values
- Modifying drug dosages to be based on a UK population
- Equalising drug administration costs for pembrolizumab and ipilimumab.

The ERG carried out two scenario analyses. In these, a subgroup of patients remains in PFS, and therefore receives treatment with pembrolizumab, for longer than that predicted by the submitted model.

Results: pembrolizumab PAS price and list prices for all other drugs

When each individual ERG amendment to the company model is made, the dominant position of pembrolizumab compared to ipilimumab for a mixed population of patients with

BRAF^{V600} wild-type and positive mutations is unaffected. This is true even if all of the ERG's changes to the company's model are adopted. In all cases, pembrolizumab continues to cost less and be more effective than ipilimumab.

When considering treatments specific to patients with BRAF^{V600} positive mutations, none of the ERG's model amendments (either singularly or combined) affect the base case position that treatment with vemurafenib is dominated by pembrolizumab, i.e. pembrolizumab continues to cost less and be more effective than vemurafenib. In terms of the comparison between pembrolizumab and dabrafenib, individually, some of the ERG's amendments do have relatively small effects on the company's cost effectiveness estimates. The largest change occurs when the ERG's preferred method of estimating treatment duration is employed (increasing the ICER by £4,584 per QALY gained). When all of the ERG's amendments are implemented together, the company's base case estimate only changes by £16 (from £5,852 to £5,868 per QALY gained). However, the ERG considers that, when comparing pembrolizumab with vemurafenib and dabrafenib, the ICERs are based on unreliable survival data.

The ERG also describes the results of an exploratory OS analysis which suggests that the OS gain from use of pembrolizumab rather than ipilimumab is only 4.1 months, less than half that estimated in the company's base case scenario (8.6 months). However, the ERG considers that even with this decrement in OS benefit, treatment with pembrolizumab is likely to dominate ipilimumab.

PAS prices for all treatments

After implementing all of the ERG's amendments using all relevant PAS prices, pembrolizumab no longer dominates ipilimumab in a mixed population of patients with BRAF^{V600} wild-type and positive mutations. Similarly, for patients with BRAF^{V600} positive mutations, pembrolizumab no longer dominates vemurafenib, and when pembrolizumab is compared with dabrafenib the ICER per QALY gained is higher than that in the original analysis. In all cases, after the ERG's amendments have been applied, the ICERs are less than £50,000 per QALY gained. However, the ERG considers that when comparing pembrolizumab with vemurafenib and dabrafenib, the estimated ICERs are based on unreliable survival data.

1.9 Cost effectiveness conclusions

Applying the full set of ERG model amendments has a limited effect on the ERG's overall assessment of cost effectiveness. However, the apparently stable estimated ICERs per

QALY gained should not be taken to indicate an absence of uncertainty as several unconvincing assumptions were employed to extrapolate data from 12 months to 30 years.

The ERG has concerns regarding the overall structure of the submitted company model. The model produces counterintuitive findings – the cost effectiveness of pembrolizumab increases as the clinical effectiveness of pembrolizumab in stopping progression decreases. In addition, the ERG considers that the true OS gain estimated by the model when comparing pembrolizumab with ipilimumab in a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations is probably 50% lower than the submitted model results suggest.

The ERG judges that, so far as the model findings can be considered valid, pembrolizumab is likely to continue to dominate ipilimumab under the PAS price for pembrolizumab even if, as the ERG suspects, the OS gain has been overestimated by 50%. The pertinent issues for consideration on the cost effectiveness of pembrolizumab compared to ipilimumab would therefore appear to be i) the likelihood that prolonged treatment on pembrolizumab would occur and ii) the PAS price for pembrolizumab.

The ERG was unable to draw cost effectiveness conclusions for the comparison of pembrolizumab with BRAF inhibitors for patients with $BRAF^{V600}$ positive mutations. This is because the ERG is not convinced that survival results generated to allow the comparison of pembrolizumab with vemurafenib and dabrafenib are valid.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Section 3.1 of the company submission[1] (CS) presents a brief overview of the disease (unresectable or metastatic melanoma) for which use of the technology (pembrolizumab) is being considered in this single technology appraisal (STA). Section 3.2 of the CS includes a description of the effects of the disease on patients, carers and society. Information about the life expectancy of people in England with the disease is presented in Section 3.4 of the CS. Key points from these sections are included in Box 1. The Evidence Review Group (ERG) considers that these points appropriately summarise the underlying health problems.

Box 1 Company's overview of unresectable or metastatic melanoma

Melanoma is a heterogeneous disease reflected by its complex pathobiology … [and] disproportionately affects a younger population than other cancers, resulting in a significant impact for patients, family and wider society.

Approximately 27% of cases diagnosed with melanoma in the UK between 2009 and 2011 were in patients aged less than 50 years, while 24% of cases affected patients aged 75 and over. This compares with 11% and 36%, respectively, when considering all cancers combined (excluding non-melanoma skin cancer).[2]

Several classifications have been developed to describe how deeply a melanoma has grown into the skin and whether it has spread to regional lymph nodes or distant (metastatic) sites at the time of initial diagnosis[3,4] … The Tumour, Node, and Metastases (TNM) staging represents the cornerstone for the management of melanoma:

- In stage III melanoma, the melanoma has spread to the lymph nodes or lymphatic channels and it may or may not be ulcerated
- In stage IV melanoma, the cancer has spread elsewhere in the body, with the brain, lung, liver, the distant lymph nodes and other areas of the skin being the most common places of metastasis.[5]

Given its life-threatening nature, a diagnosis of metastatic melanoma strongly impacts patients' life expectancy and … emotional impact can be long lasting and profound, with the most common reactions being anxiety, depression, vulnerability and a deterioration in patients' quality of life.[6-10]

The purpose of treatment for patients with unresectable or metastatic melanoma is to enable patients to resume everyday tasks and activities by slowing down the progression of disease.

Although some progress has been made in the treatment of metastatic melanoma over recent years, it still has a dismal prognosis, with a 5-year overall survival rate of between 20% and 34% for stage IIIc patients, and between 5% and 22% for patients with stage IV disease.[11]

2.2 Critique of company's overview of current service provision

A brief overview of current service provision is presented in Sections 3.3 to 3.6 of the CS. Pembrolizumab is not currently licensed for the treatment of patients with unresectable or metastatic melanoma in the UK. The estimated date of European Medicines Agency (EMA) marketing authorisation is July 2015; the company received a positive opinion from the EMA Committee for Medicinal Products for Human Use (CHMP) in May 2015.[12] Pembrolizumab is

expected to be indicated for the treatment of unresectable or metastatic melanoma in adults, with no stipulation as to whether patients must have received any previous treatment. The focus of this appraisal is patients who have not been previously treated with ipilimumab. The treatment algorithm, with the company's proposed positioning for pembrolizumab, is summarised in Figure 1.

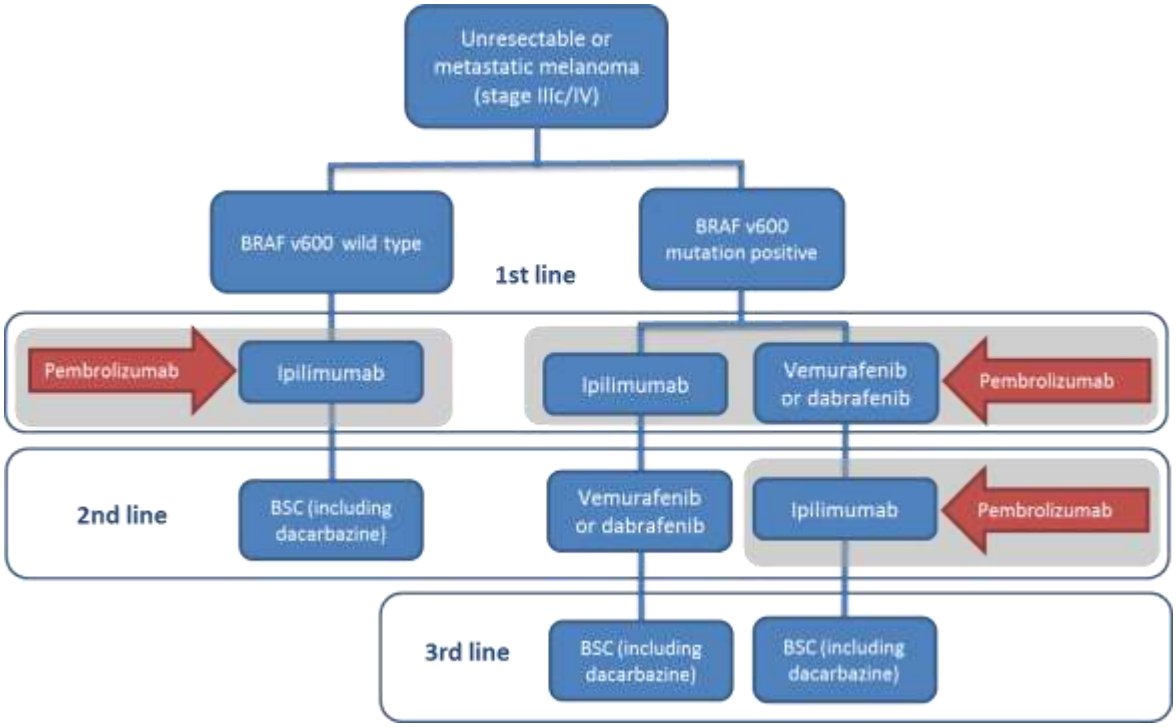


Figure 1 Treatment algorithm for unresectable or metastatic melanoma with proposed positioning for pembrolizumab presented by the company

Source: CS, Figure 3

The ERG agrees with the company (CS, page 30) that the treatment pathway for melanoma has evolved over the last 3 years, during which period positive National Institute for Health and Care Excellence (NICE) guidance has been issued in relation to the use of ipilimumab,[13,14] vemurafenib,[15] and dabrafenib.[16] The ERG also agrees that the algorithm presented by the company reflects the treatment options recommended in current NICE guidance.[13-16] The treatment options for patients with stage IIIc or stage IV (unresectable or metastatic) melanoma are currently determined by the tumour genotype. Patients identified as having $BRAF^{V600}$ (B-Raf proto-oncogene, serine/threonine kinase) mutant melanoma are eligible for first-line treatment with either a BRAF inhibitor (dabrafenib or vemurafenib) or with immunotherapy (ipilimumab).[13] For patients with $BRAF^{V600}$ wild-type mutations, ipilimumab is currently a recommended first-line treatment option.[14] The ERG agrees with the company that treatment options for patients with $BRAF^{V600}$ wild-type mutations are currently more limited than those for patients with $BRAF^{V600}$ positive mutations.

The company states that, for patients with $BRAF^{V600}$ positive mutations, there is no evidence that the effectiveness of any of the currently available treatments (ipilimumab, vemurafenib and dabrafenib) is affected by position in the treatment pathway.[17] The duration of response to BRAF inhibitors does not tend to be as long-lasting as that resulting from treatment with ipilimumab.[17,18] This is considered to be due, in part, to the ability of melanoma tumours to develop resistance to treatment, resulting in disease progression after 6 to 7 months of treatment.[18] However, patients treated with ipilimumab can take weeks, or even months, to build a complete immune response against a tumour.[19] Clinical advice to the ERG confirms that, in terms of the choice between ipilimumab and BRAF inhibitors, BRAF inhibitors tend to be preferred if a rapid response is required and ipilimumab tends to be preferred otherwise.

Regarding other systemic therapies, the company notes that dacarbazine is approved for the treatment of advanced melanoma, although its use is declining rapidly in the UK. Currently, use of dacarbazine tends to be limited to occasions when immunotherapy (such as ipilimumab and pembrolizumab), or targeted therapies (such as BRAF inhibitors), are not suitable. This, the company explains, is because dacarbazine is associated with a low level of clinical response even in treatment-naïve patients. The company cites response rates for dacarbazine (as used in the control arm of nine trials[20-28]) to be between 6.0% and 12.1%, with a median duration of response of between 6.9 months and 11.2 months. The British Association of Dermatologist guidelines[29] for the management of cutaneous melanoma state that no systemic therapy has been shown to extend survival significantly and recommend the use of dacarbazine as palliative chemotherapy. However, the guidelines were published in 2010, before the recommendation by NICE for BRAF inhibitors[15,16] and ipilimumab.[13,14] Best supportive care (BSC) implies no active systemic anti-cancer treatment. The ERG agrees that BSC is likely to be the last line of treatment for patients.

The company expects pembrolizumab to provide a durable response for a significant proportion of patients treated, and describes it as "… a step-change in the management of patients with advanced melanoma" (CS, page 31). Clinical advice received by the ERG is that pembrolizumab would be a valuable additional treatment option, particularly given the current poor prognosis of patients with unresectable or metastatic melanoma.

The company's argument to support the innovative nature of the drug is presented in Section 2.5 of the CS, and is as follows:

> "In the US, pembrolizumab was granted Breakthrough Therapy Designation for advanced melanoma by the US Food and Drug Administration (FDA)[30] in January 2013 and was granted accelerated approval in September 2014 for the treatment of patients with unresectable or

> metastatic melanoma and disease progression following ipilimumab and, if BRAF mutation positive, a BRAF inhibitor. In the UK, pembrolizumab was the first medicine to be approved under the Medicines and Healthcare Products Regulatory Agency Early Access to Medicines Scheme (EAMS). Pembrolizumab received Promising Innovative Medicines designation (EAMS Step 1) in October 2014, and in March 2015 a positive Scientific Opinion was issued (EAMS number 00025/0626)[31] for use in the treatment of unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care agents (EAMS Step 2)."

The company estimates that 1304 patients in England will be eligible for first-line treatment with pembrolizumab in 2016. The ERG agrees that the number of patients in England will be around 1304.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

This section summarises the decision problem described by the company in the CS in relation to the final scope[32] issued by NICE. A summary comparison between the final scope[32] and the CS is presented in Table 1. Each parameter in Table 1 is discussed in more detail in the text following the table.

Table 1 NICE scope and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission
Population	People with advanced (unresectable stage III or stage IV) melanoma previously untreated with ipilimumab	As per the NICE scope
Intervention	Pembrolizumab	Pembrolizumab
Comparator(s)	Dacarbazine Ipilimumab Vemurafenib (for people with $BRAF^{V600}$ mutation-positive disease) Dabrafenib (for people with $BRAF^{V600}$ mutation-positive disease)	As per the NICE scope except that the company does not consider dacarbazine to be a relevant comparator
Outcomes	The outcome measures to be considered include: PFS OS RR AEs HRQoL	As per the NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the comparator technologies should be taken into account.	Cost effectiveness is expressed in terms of an incremental cost per QALY. The time horizon considered is 30 years. Costs are considered from an NHS perspective. A range of potential PAS discounts for ipilimumab, vemurafenib and dabrafenib (in 5% increments) is considered as part of the analyses to reflect the confidential PAS prices in place
Subgroups to be considered	None	None
Other considerations	None	None

AE=adverse event; BSC=best supportive care; RR=response rate; OS=overall survival; PAS=patient access schemes; PFS=progression-free survival; QALY=quality adjusted life year
Source: CS, Table 1

3.1 Population

Pembrolizumab does not currently have a licence in Europe for patients with advanced (unresectable and metastatic) melanoma. However, in May 2015, the company received a

positive opinion from the CHMP[12] which states that pembrolizumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. It is anticipated that a licence will be issued in July 2015.

As specified in the NICE scope,[32] the population considered in the company's decision problem is patients previously untreated with ipilimumab. The ERG notes that this appraisal only considers a subset of the anticipated licensed population. Patients who have previously been treated with ipilimumab are addressed in a separate STA.[33]

The majority of the evidence included in the CS is derived from the pivotal KEYNOTE-006[34] randomised controlled trial (RCT). This trial includes patients who have received up to two systemic treatments (including adjuvant or neoadjuvant therapy) for melanoma. These treatments could have been chemotherapy, immunotherapy, a BRAF inhibitor or a mitogen-activated protein kinase (MEK) inhibitor. This means that the patient population in the KEYNOTE-006 trial includes patients who are naïve to treatment with ipilimumab, but may not be treatment-naive.

A summary of the different patient populations specified in the anticipated licence, the NICE scope,[32] the company's decision problem and the KEYNOTE-006 trial is provided in Table 2.

Table 2 Patient populations addressed in the company submission

Population for whom pembrolizumab is expected to be licensed	Population in final NICE scope	Population specified in the company's decision problem	Population included in the KEYNOTE-006 trial
Adults with advanced (unresectable or metastatic) melanoma	People with advanced (unresectable stage III or stage IV) melanoma previously untreated with ipilimumab	Adults with unresectable or metastatic melanoma previously untreated with ipilimumab	Patients with unresectable stage III or metastatic melanoma who are ipilimumab-naive; patients with BRAF mutation positive melanoma may have been previously treated with a BRAF or MEK inhibitor†

† MEK inhibitors are not currently recommended for the treatment of patients with advanced melanoma in England and Wales. In the KEYNOTE-006 trial 46% of BRAF mutation positive melanoma were pre-treated with a BRAF inhibitor

3.2 Intervention

The intervention specified in the CS and in the company's decision problem statement is pembrolizumab, an anti-programmed cell death (PD-1) agent that is administered intravenously. Different doses of pembrolizumab have been used in clinical studies.[35,36] The dose of pembrolizumab that is expected to be licensed is 2mg/kg every 3 weeks (Q3W). However, in the KEYNOTE-006 trial patients were treated with pembrolizumab 10mg/kg Q3W (or Q2W). There is no direct evidence from the KEYNOTE-006 trial to support the use

of the 2mg/kg Q3W dose of pembrolizumab in patients with advanced melanoma who are naïve to treatment with ipilimumab.

The company considers that doses of 2mg/kg Q3W and 10mg/kg Q3W are of equal efficacy. Clinical advice to the ERG is that the biological mechanism of action of pembrolizumab may explain the similarity in efficacy between the 2mg/kg and 10mg/kg doses of pembrolizumab. The ERG requested (via the clarification process) a detailed rationale from the company to support the use of the 2mg/kg dose of pembrolizumab rather than the 10mg/kg dose. In its response, the company provided the draft version of the European Public Assessment Report[37] (EPAR) issued by the EMA CHMP. The draft EPAR[37] states that, following the assessment of data from the KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006 trials, the CHMP has accepted that no differences in the efficacy of 2mg/kg and 10mg/kg are to be expected.

The ERG cautions that the numbers of patients recruited to the KEYNOTE-001 (Part D)[38] and KEYNOTE-001 (Part B1)[38] trials are relatively small and only a subset of the recruited patients were patients naïve to treatment with ipilimumab. Patients recruited to the KEYNOTE-002[39] trial had all received prior treatment with ipilimumab. This means that the trial data used in the EMA's assessment are largely derived from the outcomes of patients who have received prior treatment with ipilimumab.

3.3 Comparators

In the NICE scope,[32] dacarbazine and ipilimumab are recommended for patients with $BRAF^{V600}$ wild-type mutations and also for those with $BRAF^{V600}$ positive mutations. Vemurafenib and dabrafenib are specified only for patients with $BRAF^{V600}$ positive mutations. The company considered all the drugs listed in the NICE scope[32] as comparators, except for dacarbazine. The company explains that there is a lack of any RCTs demonstrating an improvement in survival for patients treated with dacarbazine relative to BSC. The company also cited a prospective study,[40] which included patients with advanced metastatic melanoma, and found that no clear survival benefit was apparent for patients treated with polychemotherapy (including dacarbazine) in addition to BSC, compared with BSC alone. The company's justification for excluding dacarbazine was the recent positive NICE guidance for ipilimumab,[13,14] vemurafenib[15] and dabrafenib.[16] The ERG agrees that dacarbazine is not a relevant comparator. However, the ERG notes that comparisons with dacarbazine are made in the network meta-analyses (NMAs) presentedby the company.

The company did not identify any trials that directly compare pembrolizumab with vemurafenib and dabrafenib. The company has conducted NMAs to enable the comparisons to be made.

3.4 Outcomes

Clinical evidence is reported in the CS for all five outcomes specified in the NICE scope:[32] overall survival (OS), progression-free survival (PFS), response rate (reported as overall response rate [ORR] and disease control rate), adverse events (AEs) of treatment and health-related quality of life (HRQoL). The ERG highlights that the KEYNOTE-006 trial was stopped early for benefit at the second interim analysis (IA2) on the recommendation of the Data Monitoring Committee (DMC). The company has stated that it considers the OS data from IA2 to be the definitive OS data. This means that the available OS data are immature and the true impact on OS may never be fully known. The ERG notes that there is evidence that some cancer trials which were stopped early for benefit have been shown not to reach the expected survival gain estimated at the time of stopping.[41,42] The ERG also notes that in the KEYNOTE-006 trial, the original RCT protocol stated that patients would only be treated with pembrolizumab 10mg/kg Q3W for 24 months. As the trial was stopped early, the investigators could not enforce this stopping rule. The ERG is unsure of the consequences of this course of action.

3.5 Economic analysis

As specified in the final NICE scope,[32] the cost effectiveness of treatments is expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes are assessed over a 30-year time horizon (considered equivalent to a patient's lifetime) and costs are considered from the perspective of the NHS.

3.6 Subgroups

No subgroups were specified in the final NICE scope.[32]

3.7 Other relevant factors

No equality issues were identified by the company. The ERG is aware that the company has submitted a Patient Access Scheme (PAS) application to the Department of Health. The PAS price of pembrolizumab is used in all of the cost effectiveness analyses as the Department of Health has confirmed that the PAS price is appropriate for this appraisal.

4 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical evidence submitted by the company in support of the use of pembrolizumab for the treatment of advanced melanoma previously untreated with ipilimumab.

4.1 Critique of the methods of the review

The company conducted a systematic review to identify RCTs that included pembrolizumab, in the treatment of patients with unresectable or metastatic melanoma, previously untreated with ipilimumab.

4.1.1 Searches

The search strategies used to identify studies relating to the use of pembrolizumab for the treatment of advanced melanoma are adequately described in the CS. These strategies were not specific to patients previously untreated with ipilimumab. The company conducted two systematic searches for clinical evidence: (1) a search for direct evidence and (2) a search for indirect evidence and adverse reactions. The ERG's summary and critique of the searches is reported in Appendix 1 of this ERG report. Full details of the strategies used by the company to identify clinical effectiveness evidence are reported in the CS (Section 4.1 and Appendices 2 and 7). In summary, despite the absence of potentially important databases and limiting the language to English, the ERG considers that the searches were carried out to an adequate standard and accurately reflect the population and indication of interest. The ERG is confident that no relevant studies have been missed by the company's searches.

4.1.2 Eligibility criteria

The ERG considers the company's eligibility criteria are relevant to the company's systematic review objectives.

The company used an appropriate methodology to identify relevant articles. This comprised two stages:

- **Stage 1**: The identified citations were independently assessed for inclusion through two stages, by two reviewers, using the criteria detailed in Table 3. The reviewers independently scanned all potentially eligible abstracts and conference proceedings. Full-text articles were then obtained and the same two reviewers independently reviewed these. Disagreements about whether to include a study were resolved by reaching consensus with the help of a third reviewer.
- **Stage 2**: The reviewers independently scanned all potentially eligible abstracts and conference proceedings. Full-text articles were then obtained and the same two reviewers independently reviewed these. Disagreements about whether to include a study were resolved by reaching consensus with the help of a third reviewer.

Table 3 Eligibility criteria used in the company's search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with unresectable stage III or IV melanoma, naïve to treatment with ipilimumab	Patients with non-cutaneous melanoma (i.e. ocular or mucosal melanoma) and with unknown primary site
Intervention	Pembrolizumab/MK-3475	Any other intervention
Comparators	The following treatments as monotherapy or as combination therapy • dacarbazine • ipilimumab • vemurafenib • dabrafenib	Any other comparison
Outcomes	At least one of the following outcomes: PFS OS ORR	Other efficacy and safety outcomes can be considered for analysis, but each study must include at least one of: PFS, OS or ORR
Study design	RCTs	Non-randomised clinical trials, prospective and retrospective observational studies, case studies
Language restrictions	Studies published in English language	Any other language

OS=overall survival; ORR=overall response rate; PFS=progression-free survival; RCT=randomised controlled trial
Source: CS, Table 7

4.2 Results of the company's searches

The company's search for RCT evidence identified 16 non-duplicate records from electronic databases, 15 of these were selected for full-text screening. Of the identified articles, only one met the inclusion criteria for the systematic review. The company identified one other relevant trial from searches of www.clinicaltrials.gov, conference abstracts and the company's own records.

The company's search for non-RCT evidence identified one record from the electronic databases that were interrogated.

A further five[22,25,28,43-45] trials met the inclusion criteria for the NMAs. The company's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, which shows how many articles were excluded at each step of the inclusion process is presented in the CS (page 43).

4.3 Identified studies

One RCT (KEYNOTE-006) was identified by the company as being relevant to a systematic review designed to assess the clinical effectiveness of pembrolizumab.

The company also identified data from KEYNOTE-001 (Part D) and KEYNOTE-0001 (Part B) to be relevant to the decision problem.

The company focuses on presenting evidence from the KEYNOTE-006 trial. This trial compares two different dosing regimens of pembrolizumab (10mg/kg Q3W and 10mg/kg Q2W) with treatment with ipilimumab. The ERG considers that the KEYNOTE-006 trial is the only trial of direct relevance to the decision problem, despite not including the 2mg/kg Q3W dose of pembrolizumab. The ERG is not aware of any other studies relevant to the present appraisal.

4.3.1 Critique of data extraction

Relevant data were extracted by one reviewer and checked by a second reviewer. Any inconsistencies were resolved through discussion. The ERG considers this to be good standard practice.

4.3.2 Quality assessment

A critical appraisal of the included studies was conducted by the company using assessment criteria based on the recommendations included in the NICE STA Methods Guide.[46]

4.3.3 Evidence synthesis

Since only the KEYNOTE-006 trial directly compared pembrolizumab with an appropriate comparator (ipilimumab), findings were appropriately presented in a narrative synthesis.

In the absence of direct evidence comparing pembrolizumab with three of the comparators specified in NICE's final scope,[32] the company has conducted a series of network meta-analyses.

4.4 ERG critique of direct evidence of clinical effectiveness

Details of the KEYNOTE-006 trial are described in a paper[36] published in 2015. The information relevant to the KEYNOTE-006 trial presented in this ERG report is taken from documents provided by the company as part of its submission to NICE.

4.4.1 Characteristics of the KEYNOTE-006 trial

The key characteristics of the KEYNOTE-006 trial are summarised in Table 4. This trial was conducted internationally and randomised 834 patients in a 1:1:1 ratio to pembrolizumab 10mg/kg Q2W, pembrolizumab 10mg/kg Q3W and ipilimumab 3mg/kg Q3W. Randomisation was stratified by ECOG (Eastern Cooperative Oncology Group) performance status (0

versus 1), line of prior therapy (first versus second) and PD-L1 (Programmed cell death 1 ligand) expression status (high versus low expression).

Eligibility criteria for entry into the KEYNOTE-006 trial are provided by the company (CS, pages 49 to 51). Clinical advice to the ERG is that the eligibility criteria are reasonable and that the trial population is representative of the patient population seen in clinical practice in England and Wales.

The ERG considers that the KEYNOTE-006 trial was well-designed and conducted and notes the inclusion in the trial of patients from treatment centres based in the UK.

Table 4 Characteristics of the KEYNOTE-006 trial

Characteristics of the KEYNOTE-006 trial	
Location	Global study conducted in 16 countries (Australia, Austria, Belgium, Canada, Chile, Colombia, France, Germany, Israel, Netherlands, New Zealand, Norway, Spain, Sweden, UK and USA)
Design	Randomised, controlled, open-label, three-arm, phase III study
Population	Histologically confirmed diagnosis of unresectable stage III or metastatic melanoma not amenable to local therapy Patients who have not received prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (first line) or who have received one prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (second line) are both eligible Patients must have testing for a BRAF mutation prior to study entry. Patients with $BRAF^{V600}$ mutant melanoma may have received prior BRAF inhibitor therapy as first-line systemic therapy and be eligible in this study for second- line treatment. At the discretion of the investigator, patients with $BRAF^{V600}$ mutation positive melanoma who have NOT received a BRAF inhibitor are also eligible for this study as first-line treatment if they meet additional criteria (CS, Section 4.3.1)
Intervention and comparator	Pembrolizumab 10 mg/kg Q2W (n=279) Pembrolizumab 10 mg/kg Q3W (n=277) Ipilimumab 3 mg/kg Q3W (total of 4 doses) (n=278)
Primary outcomes	PFS OS
Secondary outcomes	ORR OS, PFS, and ORR in the subgroup of patients with high PD-L1 expression level Safety, tolerability and AE profile of pembrolizumab versus ipilimumab
Duration of study	The study commenced in September 2013, and completed enrolment in March 2014. The data-cut-off date for IA1 was September 03, 2014 with the exception of OS (data cut-off date 03 March, 2015, IA2). The study was stopped early for efficacy on the recommendation of the Data Monitoring Committee (DMC). The final analysis will be performed when approximately 435 deaths have occurred across three arms, or all patients have been followed up for 21 months, whichever occurs first.

AE=adverse event; IA1=first interim analysis; IA2=second interim analysis; ORR=overall response rate; OS=overall survival; PD-L1=programmed cell death 1 ligand; PFS=progression-free survival
Source: CS, Table 10 and Section 4.2.1

4.4.2 Patient characteristics

The characteristics of patients included in the KEYNOTE-006 trial are summarised in Table 5. The ERG agrees with the company that the patient characteristics appear to be well-balanced across the treatment groups. However, the ERG notes that 22 patients in the

ipilimumab arm did not start treatment; all of the patients who were randomised to pembrolizumab 10mg/kg Q3W received treatment.

Table 5 Baseline characteristics of patients recruited to the KEYNOTE-006 trial

Patient characteristic	KEYNOTE-006: ITT population		
	Pembrolizumab 10mg/kg Q2W	Pembrolizumab 10 mg/kg Q3W	Ipilimumab 3 mg/kg Q3W
N	279	277	278
Male (%)	57.7	62.8	58.3
Age, median (range)	61 (18-89)	63 (22-89)	62 (18-88)
ECOG PS (%)			
0	70.3	68.2	67.6
1	29.7	31.8	32.4
M1c stage at entry (%)	64.2	68.2	63.7
$BRAF^{V600}$ mutation (%)	35.1	35.0	38.5
Brain metastasis (%)	8.2	9.7	10.1
Previous lines of treatment (%)			
0	65.6	66.8	65.1
1	34.4	32.9	34.9
2	0	0.4	0
Elevated LDH (%)	29.0	35.4	32.7
Median baseline tumour burden (mm) (range)	57.5 (11-390)	61.7 (11-554)	55.2 (10-465)

ECOG PS=Eastern Cooperative Oncology Group Performance Status; ITT=intention-to-treat; LDH=lactate dehydrogenase; Q2W= every 2 weeks; Q3W=every 3 weeks
Source: CS, Table 17

4.4.3 Statistical approach adopted

Information relevant to the statistical approach taken by the company to analyse data from the KEYNOTE-006 trial are taken from the CSR,[34] the trial protocol,[36] and the CS.

Trial population

The intention-to-treat (ITT) population was used to determine PFS, OS and ORR results. All patients were analysed according to the treatment group to which they were initially randomised, regardless of which treatment they actually received. All safety data analyses were performed using the 'All Patients as Treated' (APaT) population, consisting of all randomised patients who received at least one dose of study treatment.

Outline of analyses

An outline of the planned interim analyses, interim analysis 1 (IA1) and interim analysis 2 (IA2), and their purposes is provided in Table 6. The company states that the KEYNOTE-006 trial was stopped for efficacy after 12 months and is therefore no longer recruiting patients.

Table 6 Summary of the strategies used for KEYNOTE-006 interim analyses

	Interim analysis 1 (Primary analysis of PFS)	**Interim analysis 2**
Endpoints	PFS and OS	PFS and OS
Approximate timing	All patients followed up for 6 months and approximately 260 PFS events have been observed across the three arms	When minimum follow-up is at least 9 months and approximately 290 deaths have been observed unless it takes longer than 12 months of follow-up to observe 290 deaths in which case, the analysis will be performed when minimum follow-up is12 months
Sample size on which the primary analysis is based	Approximately 260 PFS events and approximately 235 deaths across three arms	Approximately 440-485 PFS events, approximately 290 deaths across three arms
Stop early for futility[a]	PFS does not meet the efficacy bar AND the OS improvement is <1 month (empirical OS HR>0.9167[c]) for both pembrolizumab arms	Not applicable
Stop early for efficacy	(one-sided) p-value for OS <0.002% for both pembrolizumab arms or p-value <0.001% for one pembrolizumab arm (corresponds to empirical HR <0.5223 or 0.5095, median OS improvement >10.1 or 10.6 months respectively[c,d])	(one-sided) p-value <0.5% for both pembrolizumab arms or p-value <0.25% for one pembrolizumab arm (corresponds to empirical HR <0.6947 or 0.6724, median OS improvement >4.8 or 5.2 months respectively[3,4])
Efficacy bar at IA1 (primary analysis of PFS)	(one-sided) p-value for PFS <0.2% for at least one pembrolizumab arm (corresponds to empirical HR 0.6511, median PFS improvement >1.6 months[b])	Not applicable

a Totality of data will be reviewed to determine whether the study will be terminated or halted
b Assume median PFS in the control arm is 3 months. Estimates of empirical effect in brackets are approximates
c Assume median survival time in the control arm is 11 months. Estimates of empirical effect in brackets are approximates
d Hochberg step-up procedure will be used for OS testing at both the second interim analysis and the final analysis, giving equal weight to the two pembrolizumab arms, if neither is discontinued prior to the analyses
DMC=Data Monitoring Committee; HR=hazard ratio; OS=overall survival; PFS=progression-free survival
Source: CS, Table 11

The company states (CS, page 87) that "…as OS was positive at IA2, no formal OS analysis will be conducted at the planned final analysis. However, patients will continue to be followed up and long-term survival for this study will be updated as deemed appropriate." The ERG considered the company's position to be unclear and requested further explanation via the clarification process. In its response, the company stated:

> "At the second interim analysis (IA2), the Data Monitoring Committee (DMC) considered that KEYNOTE-006 had met its primary endpoints so they recommended the study stop early and considered the IA2 to be the definitive OS analysis. The use of other PD-1 treatments after discontinuation of ipilimumab is likely to underestimate the true survival benefit of pembrolizumab over ipilimumab (since it may bias HR towards the null). Patients will continue to be followed up and the company agrees [with the DMC] that, although the final OS analysis will not change the conclusions regarding the positive survival effect of pembrolizumab, it will provide important insight into how the crossover to other treatments may have underestimated the OS findings. Exploratory analysis adjusting for subsequent anti-cancer therapy will be

provided at the final analysis of OS, this is expected to be completed in the second half of 2016. The exact time for this analysis is not yet known, since it is event driven."

The ERG is concerned that the KEYNOTE-006 trial was stopped early for benefit. Early closure of trials may lead to exaggerated treatment effects that are not borne out in the longer term.[41,42,47,48] As the trial has now been stopped, no formal OS analysis will be conducted at the planned final analysis. The ERG considers that the strength of evidence submitted in support of pembrolizumab would be improved if data from the final analysis were to be made available as initially planned.

Efficacy outcomes

The definitions and methods of analysis used to generate primary and secondary efficacy outcome results from the KEYNOTE-006 trial are presented in Table 7.

Table 7 Analysis strategy used to generate key efficacy endpoints (KEYNOTE-006 trial)

Endpoint	Definition	Statistical method
Primary outcomes		
PFS and OS	Time from randomisation to the first documented disease progression or death due to any cause, whichever occurs first	Testing: stratified log-rank test used to assess treatment difference in PFS Estimation: stratified Cox proportional hazard model with Efron's method of tie handling used to assess magnitude of treatment difference between the treatment arm (HR and its 95% CI reported) K-M method for PFS curve estimation in each treatment group
Secondary outcome		
ORR	Proportion of the patients in the analysis population who have best response as CR or PR	Stratified Mietten & Nurminen method

CI=confidence interval; CR=complete response; HR=hazard ratio; K-M=Kaplan-Meier; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response;
Source: CS, Table 13

The stratified log-rank test and stratified Cox model used the randomisation stratification factors of: line of prior therapy (first versus second), PD-L1 expression status (high versus low) and ECOG performance status (0 versus 1).

The company states that as progressive disease could occur at any point between assessments, the date of progressive disease was approximated as the date of the first assessment at which progressive disease was objectively documented using RECIST 1.1 criteria, regardless of study drug discontinuation.

The ERG is satisfied that all outcomes were pre-specified in the trial SAP[34] and were fully reported in the CSR.[34]

Censoring methods

For the primary analysis, patients without documented death at the time of the final analysis were censored at the date of the last follow-up. Three sensitivity analyses were carried out to investigate the robustness of the PFS endpoint, using alternative censoring rules. The company provides a summary of the censoring rules for primary and sensitivity analyses in Table 15 of the CS.

ERG assessment of statistical approach

A summary of the ERG's assessment of the statistical approach used to analyse data from the KEYNOTE-006 trial is presented in

Table 8.

Table 8 ERG assessment of the statistical approach used to analyse KEYNOTE-006 trial data

Component	Statistical approach	ERG comments
Sample size calculation	Provided in the CS (pages 63 and 64)	The ERG considers that the methods used to calculate the sample size are correct
Protocol amendments	Provided in the CSR[34] (Section 9.7.1)	The ERG notes that the changes detailed in the protocol amendments[34] were unlikely to have been driven by the results of the trial and are therefore not a cause for concern
Missing data approach	The company reports that a model-based approach was used to handle missing data for both OS and PFS. For ORR, patients with missing data were considered to be non-responders	The ERG is satisfied that the company took a suitable approach to handling missing data
Subgroup analyses for OS and PFS	• Pre-specified subgroup analyses: • Age category (≤65 versus.>65 years) • Sex (female versus male) • Race (white versus non-white) • ECOG status (0 versus 1) • Line of therapy (first versus second) • Prior treatment with a BRAF or MEK inhibitor (yes versus no) • BRAF mutation status • Region (US versus non-US) • PD-L1 expression (high versus low) (depending on assay availability) • Human leukocyte antigen (HLA-A*0201) (positive versus negative) (depending on availability of data) • Prior immunotherapy such as interferon, peg-interferon, and IL-2 (yes versus no)	The ERG is satisfied that the results of all subgroup analyses are provided in the CS/CSR[34]
Sensitivity analyses for the primary outcome	Pre-specified sensitivity analyses in the SAP:[34] PFS using three different sets of censoring rules PFS analysis using time to scheduled tumour assessment. OS analysis that censors patients at the time of initiation of new therapy	The ERG notes that the PFS related sensitivity analysis results are provided in the CSR[34] but has been unable to identify results from any sensitivity analyses relating to OS

CS=company submission; CSR=clinical study report; ECOG=Eastern Cooperative Oncology Group; ERG=Evidence Review Group; ORR=overall response rate; OS=overall survival; PD-L1=programmed cell death 1 ligand; PFS=progression-free survival; SAP=statistical analysis plan; US=United States
Source: CS and ERG comment

4.4.4 Risk of bias assessment for KEYNOTE-006

The company conducted a risk of bias assessment for the KEYNOTE-006 trial using the criteria recommended in the NICE methods Guide[49] (Table 9).

The ERG agrees with the company's assessment for the majority of criteria. However, the ERG considers that, as randomisation was conducted centrally using an interactive voice response system (IVRS), the concealment of treatment allocation was adequate. The use of the IVRS ensures that a patient's allocation to a particular treatment arm could not be predicted or influenced. The ERG also notes that an element of blinding was in place in the KEYNOTE-006 trial as the analyses of PFS and ORR were based on blinded independent central review.

Detail provided in the CS shows that 22 patients randomised to the ipilimumab arm of the KEYNOTE-006 trial withdrew consent prior to treatment. In contrast, none of the patients randomised to receive pembrolizumab 10mg/kg Q3W withdrew consent. The ERG notes that the 22 patients who withdrew consent are accounted for in the final analyses. Overall, the ERG considers that the risk of bias for the KEYNOTE-006 trial is low. However, the ERG notes that the KEYNOTE-006 trial was stopped early for benefit. It is unclear what impact the early closure will have on the final OS results of the trial.

Table 9 Company's assessment of risk of bias for KEYNOTE-006 with ERG comments

Risk of bias criteria	KEYNOTE-006	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	Not applicable	Disagree Patients were randomised via IVRS and therefore treatment allocation was concealed
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Analyses of PFS and ORR were conducted by blinded independent central review
Were there any unexpected imbalances in drop-outs between groups?	Yes	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree
Did the analysis include an intention-to-treat analysis? Was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree

IVRS=interactive voice response system; ORR=overall response rate; PFS=progression-free survival
Source: CS, Table 19

4.5 Results from the KEYNOTE-006 trial

PFS results (IA1) and OS results (IA1 and IA2) from the KEYNOTE-006 trial are reported in this section. A summary of the ORR results at these time points is provided in Section 4.7 of the CS. The ERG notes that IA1 and IA2 were conducted after a follow-up of 6-months and 12-months respectively.

Results for patients included in both the pembrolizumab arms (10mg/kg Q3W and 10mg/kg Q2W) are presented in the tables and figures in the CS. The company considers, and the ERG agrees, that the frequency at which the dose is delivered does not affect efficacy. This ERG report only includes results for patients treated every 3 weeks as this is the treatment frequency expected to be approved in the anticipated licence.

The analyses carried out by the company to generate PFS and OS hazard ratios are conducted using Cox proportional hazards modelling. To test the assumption of proportional hazards the Schoenfeld[50] residuals method was used. The ERG is of the opinion that the proportional hazards assumption ought to have been validated for the first 12 weeks as well as from 13 weeks onwards in order to verify that an appropriate method had been used to analyse the PFS data. In addition, the ERG carried out an alternative method of testing proportional hazards and concluded that the assumption of proportional hazards was violated for PFS and OS.

Other treatments received

The company states that an exploratory OS analysis, adjusting for subsequent anti-cancer therapy, was not performed as part of IA1 or IA2. At the time of IA2, OS benefit was found to be statistically significantly better for patients in both pembrolizumab arms versus ipilimumab at the pre-specified alpha level of 0.005 using the Hochberg step-up procedure without adjusting for non-study treatment.

The ERG requested additional information from the company (via the clarification process) regarding the other treatments patients received following discontinuation of their randomised treatment. The results provided by the company suggest that, compared to treatment with pembrolizumab, more patients treated with ipilimumab started on a new anti-cancer therapy. The ERG notes that there is substantial variation in the follow-on treatments given to patients; however clinical advice to the ERG is that this is not a cause for concern.

4.5.1 Progression-free survival

Central (IRO) assessment results

The company's PFS results are provided in Table 10 and Table 11. The results are based on central integrated radiology and oncology analysis (IRO) assessment using the Response Evaluation Criteria in Solid Tumours 1.1[51] criteria. When comparing ipilimumab and pembrolizumab treatment, pembrolizumab 10mg/kg Q3W is shown to have a significant effect on PFS (HR=0.58; 95% CI 0.47 to 0.72, p<0.0001). The difference in median PFS between the treatment arms is 1.3 months; median PFS is 4.1 months in the pembrolizumab 10mg/kg Q3W arm and 2.8 months in the ipilimumab arm (Table 10). The company highlights that treatment benefit persists beyond 6 months, as demonstrated by the PFS rates at 3, 6, 9, and 12 months; these data are summarised in Table 11.

Table 10 PFS results based on central (IRO) assessment using the primary censoring rule and ITT population in KEYNOTE-006 (RECIST 1.1 criteria)

Treatment arm	Number of events (%)	Person-months	Event rate/100 person-months (%)	Median PFS† (months) (95% CI)	PFS rate at month 6 in %† (95% CI)	Treatment vs ipilimumab HR (95% CI)‡ p-value§
Ipilimumab 3mg/kg n=278	188 (67.6)	910.9	20.6	2.8 (2.8 to 2.9)	26.5 (20.9 to 32.4)	---
Pembrolizumab 10mg/kg Q3W n=277	157 (56.7)	1303.1	12.0	4.1 (2.9 to 6.9)	46.4 (40.3 to 52.3)	0.58 (0.47 to 0.72) p<0.0001
Pembrolizumab 10mg/kg Q2W n=279	157 (56.3)	1334.4	11.8	5.5 (3.4 to 6.9)	47.3 (41.2 to 53.2)	0.58 (0.46 to 0.72) p<0.0001

CI=confidence interval; HR=hazard ratio; IRO=integrated radiology and oncology analysis (central assessment); ITT=intention-to-treat; PFS=progression-free survival; Q2W=every 2 weeks; Q3W=every 3 weeks
† From product-limit (K-M) method for censored data
‡ Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (high positive vs low positive) and ECOG (0 vs 1)
§One-sided p-value based on log-rank test
Source: CS, Table 22

Table 11 PFS rate over time based on central (IRO) assessment and ITT population in KEYNOTE-006 (RECIST 1.1 criteria)

PFS rate %† (95% CI)	Ipilimumab 3mg/kg (n=278)	Pembrolizumab 10mg/kg Q3W (n=277)	Pembrolizumab 10mg/kg Q2W (n=279)
3 months	40.9 (34.7 to 47.0)	55.7 (49.5 to 61.4)	58.3 (52.2 to 64.0)
6 months	26.5 (20.9 to 32.4)	46.4 (40.3 to 52.3)	47.3 (41.2 to 53.2)
9 months	16.0 (10.3 to 22.7)	41.6 (35.3 to 47.8)	40.3 (33.6 to 46.8)
12 months	---	14.9 (1.7 to 41.0)	19.0 (5.3 to 39.0)

CI=confidence interval; IRO=integrated radiology and oncology analysis; ITT=intention-to-treat; PFS=progression-free survival; Q2W=every 2 weeks; Q3W=every 3 weeks
† From product-limit (K-M) method for censored data
Source: CS, Table 23

Local investigator assessment results

The local investigator (INV) PFS results are presented in Table 12. The assessments were made using the Immune-related Response Criteria.[52] The INV are similar to those based on the central IRO assessment (HR=0.56; 95% CI 0.45 to 0.70, p<0.0001). Median PFS was 7.2 months for pembrolizumab 10mg/kg Q3W and 3.3 months in the ipilimumab arm. The company highlights that treatment benefit persists beyond 6 months, as demonstrated by the PFS rates at 3, 6, 9, and 12 months; these data are summarised in Table 13.

Table 12 PFS based on investigator assessment (ITT population) in KEYNOTE-006 (irRC criteria)

Treatment arm	Number of events (%)	Person-months	Event rate/100 person-months (%)	Median PFS† (months) (95% CI)	PFS rate at month 6 in %† (95% CI)	Treatment vs ipilimumab HR (95% CI)‡ p-value§
Ipilimumab 3mg/kg n=278	177 (63.7)	1047.0	16.9	3.3 (2.9 to 4.2)	33.6 (27.6 to 39.7)	---
Pembrolizumab 10mg/kg Q3W n=277	145 (52.3)	1486.9	9.8	7.2 (5.6 to 9.7)	55.0 (48.8 to 60.7)	0.56 (0.45 to 0.70) p<0.0001
Pembrolizumab 10mg/kg Q2W n=279	142 (50.9)	1468.1	9.7	7.0 (5.6 to 9.6)	54.5 (48.3 to 60.3)	0.56 (0.45 to 0.70) p<0.0001

CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; PFS=progression-free survival; Q2W=every 2 weeks; Q3W=every 3 weeks
† From product-limit (K-M) method for censored data
‡ Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (high positive vs low positive) and ECOG (0 vs 1); if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison
§ One-sided p-value based on stratified log-rank test
Source: CS, Table 24

Table 13 PFS rate over time based on investigator assessment (ITT population) in KEYNOTE-006 (irRC criteria)

PFS rate %† (95% CI)	Ipilimumab 3mg/kg (n=278)	Pembrolizumab 10mg/kg Q3W (n=277)	Pembrolizumab 10mg/kg Q2W (n=279)
3 months	51.5 (45.0 to 57.6)	66.5 (60.5 to 71.7)	67.4 (61.5 to 72.6)
6 months	33.6 (27.6 to 39.7)	55.0 (48.8 to 60.7)	54.5 (48.3 to 60.3)
9 months	20.2 (14.0 to 27.2)	45.1 (38.1 to 51.8)	44.4 (37.4 to 51.2)
12 months	---	11.5 (1.3 to 34.0)	---

CI=confidence interval; ITT=intention-to-treat; PFS=progression-free survival; Q2W=every 2 weeks; Q3W=every 3 weeks
† From product-limit (K-M) method for censored data
Source: CS, Table 25

Sensitivity analyses

The company reports that results from PFS sensitivity analyses using three different censoring approaches and using time to scheduled tumour assessment were consistent with the results from the primary PFS analysis. The ERG agrees with the company's conclusion.

Subgroup analyses

No subgroups were specified in the NICE final scope.[32] All subgroup analyses undertaken by the company are listed in

Table 8 of this ERG report and the results are available in Appendix 6 of the CS.

Of note are the results from the analyses which suggest that, in comparison to ipilimumab, the efficacy of pembrolizumab was greater in both the PD-L1 positive (HR=0.52) and PD-L1 negative (HR=0.76) subgroups. However, the p-value for the test for subgroup differences was not statistically significant.

Efficacy was found to be consistent across all other subgroups; no statistically significant p-values for interaction were observed with the exception of line of systemic therapy. The results of the tests for subgroup differences were provided by the company during the clarification process.

4.5.2 Overall survival results

Interim analysis 1

The results of the ITT population OS analysis at IA1 are provided in Table 14.

At the time these analyses were undertaken a total of 202 patients had died, representing 46% of the target number of events at final analysis (435 deaths). The results of IA1 favour the pembrolizumab 10mg/kg Q3W arm in terms of OS (HR=0.56; 95% CI 0.40 to 0.78, p=0.0003). None of the medians had been reached at the time of the IA1 analysis.

Table 14 Analysis of overall survival at IA1 for the ITT population

Treatment arm	Number of events (%)	Person-months	Event rate/100 person-months (%)	Median OS† (months) (95% CI)	OS rate at month 6 in %† (95% CI)	Treatment vs ipilimumab HR (95% CI)‡ p-value§
Ipilimumab 3mg/kg n=278	85 (30.6)	1767.4	4.8	Not reached	74.6 (68.8 to 79.5)	---
Pembrolizumab 10mg/kg Q3W n=277	56 (20.2)	2043.1	2.7	Not reached	87.6 (83.1 to 91.0)	0.56 (0.40 to 0.78) p=0.00031
Pembrolizumab 10mg/kg Q2W n=279	61 (21.9)	2034.9	3.0	Not reached	84.8 (80.0 to 88.5)	0.60 (0.43 to 0.84) p=0.00132

CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; OS=overall survival; Q2W=every 2 weeks; Q3W=every 3 weeks
† From product-limit (K-M) method for censored data
‡ Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative) and ECOG (0 vs 1); if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison
§ One-sided p-value based on stratified log-rank test
Source: CS, Table 26

At the time that the IA1 analyses were undertaken, none of the differences in length of OS between the trial arms was found to be statistically significant at the pre-specified alpha level of 0.00002. There was, therefore, no reason to stop the trial early for efficacy. The investigators continued to follow up patients as recommended by the DMC and a second interim analysis (IA2) was performed as pre-specified in the study protocol.

Interim analysis 2

The primary objective of IA2 was to evaluate treatment effect based on OS. This analysis was performed after 12 months of follow-up was complete as the number of deaths was <290. A total of 289 patients had died by the time IA2 was undertaken, representing 66% of the target number of events at final analysis (435 deaths). Patients who were still alive after the IA2 data cut-off date (03 March 2015) were censored on this date.

The OS results, for the ITT population, from the IA2 analysis are provided in Table 15. Compared to the ipilimumab arm, these results favour the pembrolizumab 10mg/kg Q3W arm at the pre-specified alpha level of 0.005 (HR=0.69; 95% CI 0.52 to 0.90, p=0.0036). At the time that the IA2 analyses were undertaken the median OS had still not been reached.

The company suggests that substantial treatment benefit persists beyond 6 months, as demonstrated by the OS rates at 4, 6, 12 and 15 months; these data are summarised in Table 16.

Table 15 Analysis of OS for the ITT population at IA2

Treatment arm	Number of events (%)	Person-months	Event rate/100 person-months (%)	Median OS† (months) (95% CI)	OS rate at month 6 in %† (95% CI)	Treatment vs Ipilimumab HR (95% CI)‡ p-value§
Ipilimumab 3mg/kg n=278	112 (40.3)	2572.3	4.4	Not reached (12.7 to…)	74.5 (68.7 to 79.4)	---
Pembrolizumab 10mg/kg Q3W n=277	92 (33.2)	3105.7	3.0	Not reached	87.3 (82.7 to 90.7)	0.69 (0.52 to 0.90) p=0.00358
Pembrolizumab 10mg/kg Q2W n=279	85 (30.5)	3152.8	2.7	Not reached	84.8 (80.0 to 88.5)	0.63 (0.47 to 0.83) p=0.00052

CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; OS=overall survival; Q2W=every 2 weeks; Q3W=every 3 weeks
† From product-limit (K-M) method for censored data
‡ Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative) and ECOG (0 vs 1); if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison
§ One-sided p-value based on stratified log-rank test
Source: CS, Table 27

Table 16 OS rate over time (ITT population) in the KEYNOTE-006 trial

OS rate %† (95% CI)	Ipilimumab 3mg/kg (n=278)	Pembrolizumab 10mg/kg Q3W (n=277)	Pembrolizumab 10mg/kg Q2W (n=279)
4 months	83.2 (78.0 to 87.3)	92.0 (88.1 to 94.7)	90.2 (86.1 to 93.2)
6 months	74.5 (68.7 to 79.4)	87.3 (82.7 to 90.7)	84.8 (80.0 to 88.5)
12 months	58.2 (51.8 to 64.0)	68.4 (62.5 to 73.6)	74.1 (68.5 to 78.9)
5 months	53.1 (45.9 to 59.7)	64.0 (57.3 to 69.9)	62.8 (54.8 to 69.7)

CI=confidence interval; ITT=intention-to-treat; OS=overall survival; Q2W=every 2 weeks; Q3W=every 3 weeks

† From product-limit (K-M) method for censored data
Source: CS, Table 28

The ERG has concerns about the early termination of the KEYNOTE-006 trial which occurred after IA2 as OS results were positive. The ERG considers that the strength of evidence submitted for pembrolizumab would be improved if data from the planned final analysis were available.

Subgroup analyses

In the PD-L1 positive subgroup, the OS result for combined pembrolizumab arm is more favourable than that for the ipilimumab arm (HR=0.58]). However, for the PD-L1 negative subgroup, there was no OS benefit for those treated with pembrolizumab compared to those treated with ipilimumab (HR=1.02). None of the p-values for interaction, for all performed subgroup analyses (provided as part of the clarification process), was significant.

4.6 Health-related quality of life from the KEYNOTE-006 trial

The company states (CS, page 90) that HRQol outcomes were measured during the KEYNOTE-006 trial using the European Organisation for Research and Treatment Cancer Quality of Life Questionnaire[53] (EORTC QLQ-C30) and the EuroQol EQ5D[54] tool. The company reports that at the time it sent its submission to NICE, the results from the EORTC QLQ-C30 were not available. However, the results from the EQ-5D tool were available and have been used to inform the company's cost effectiveness analysis. The company states (CS, page 186) that the percentage of EQ-5D questionnaires available for analysis at IA1 from the patients treated with pembrolizumab 10mg/kg Q3W and patients treated with ipilimumab was 68% and 53% respectively. The company found no significant difference in HRQoL for patients treated with pembrolizumab and patients treated with ipilimumab.

4.7 Adverse events reported in the KEYNOTE-006 trial

In Section 4.12 of the CS, the company describes safety data from KEYNOTE-006. The company states that the safety population reported in the CS is the APaT population. These data were collected up to the time of IA1 (i.e. at a follow-up of 6 months and 260 PFS events) and AEs were recorded from the first study treatment until 30 days after the last study treatment. Data relating to serious AEs (SAEs) were followed up to 90 days after the last study treatment.

Treatment exposure

Information in Table 17 shows that the mean number of treatments given to patients in the pembrolizumab 10mg/kg Q3W arm was eight, whilst the mean number of treatments for patients in the ipilimumab arm was 3.3. The company reports that the number of ipilimumab treatments is in accordance with the protocol-planned four treatments. The company highlights that treatment duration for patients in both the pembrolizumab arms was three times longer than that of patients in the ipilimumab arm of the trial (mean of 51 days vs 164 days).

Table 17 Summary of drug exposure (KEYNOTE-006)

	Ipilimumab 3mg/kg n=256	Pembrolizumab 10mg/kg Q3W n=277	Pembrolizumab 10mg/kg Q2W n=278
Days on treatment mean (SD)	50.94 (27.64)	163.88 (90.75)	163.93 (90.73)
Number of administrations mean (SD)	3.29 (0.99)	8.00 (4.26)	12.00 (5.89)

Q2W=every 2 weeks; Q3W=every 3 weeks; SD=standard deviation
Source: CS, Table 55

Adverse events summary

The company provides a summary of broad AE categories by treatment arm (Table 18). The ERG agrees that treatment with pembrolizumab appears to be well-tolerated and is associated with similar rates of AEs to treatment with ipilimumab. The ERG also agrees with the company that patients treated with pembrolizumab experienced fewer grade 3 to 5 AEs, SAEs, drug-related SAEs and SAEs leading to treatment discontinuation compared to patients treated with ipilimumab. However, the ERG notes the high frequency of drug-related AEs in both arms of the trial (73%).

The company also provides evidence (CS, Table 57) that the time to onset of grade 3 to 5 AEs was statistically significantly longer for patients treated with pembrolizumab compared with that for patients treated with ipilimumab (mean time to AE=88 days and 42.4 days respectively [HR=0.52; 95% CI 0.38 to 0.72, p<0.001]).

Table 18 Adverse events in the KEYNOTE-006 trial

Type of adverse event	Ipilimumab 3mg/kg n=256	Pembrolizumab 10mg/kg Q3W n=277	Pembrolizumab 10mg/kg Q2W n=278
	n (%)	n (%)	n (%)
One or more AE	239 (93.4)	264 (95.3)	275 (98.9)
No AE	17 (6.6)	13 (4.7)	3 (1.1)
Drug-related† AE	187 (73.0)	202 (72.9)	221 (79.5)
Toxicity grade 3 to 5 AE	94 (36.7)	92 (33.2)	105 (37.8)
Toxicity grade 3 to 5 drug-related AE	51 (19.9)	28 (10.1)	37 (13.3)
Serious AE	77 (30.1)	69 (24.9)	71 (25.5)
Serious drug-related AE	45 (17.6)	18 (6.5)	31 (11.2)
Death	3 (1.2)	5 (1.8)	7 (2.5)
Death due to a drug-related AE	1 (0.4)	0 (0.0)	1(0.4)*
Discontinuation‡ due to AE	34 (13.3)	30 (10.8)	20 (7.2)
Discontinuation due to drug-related AE	24 (9.4)	19 (6.9)	11 (4.0)
Discontinuation due to serious AE	25 (9.8)	23 (8.3)	18 (6.5)
Discontinuation due to serious drug-related AE	19 (7.4)	12 (4.3)	9 (3.2)

AE=adverse event; Q2W=every 2 weeks; Q3W=every 3 weeks
†=investigator–determined
‡=study medication withdrawn
*One drug-related death is listed against the pembrolizumab 10 mg/kg Q2W arm, but the investigator changed the assessment of causality from related to unrelated after the database lock for the current analysis
Source: CS, Table 56

Treatment-related adverse events

The company provides a list of AEs reported by ≥1% of patients that were considered to be related to study treatment (possibly, probably or definitely). The full list of AEs is presented in the CS (Table 58).

For patients treated with pembrolizumab, the most frequently reported AEs of any grade were fatigue (19%), diarrhoea (14.4%), pruritus (14.1%), rash (13.4%), arthralgia (11.6%), asthenia (11.2%), nausea (11.2%) and vitiligo (11.2%). Grade 3 to 5 diarrhoea was experienced by more than 1% of patients.

For patients treated with ipilimumab, the most frequently reported AEs of any grade were fatigue (15.2%), diarrhoea (22.7%), pruritus (25.4%), rash (14.5%), nausea (8.6%) and asthenia (6.3%). Grade 3 to 5 diarrhoea and fatigue was experienced by more than 1% of patients.

Immune-related AEs

The company presents an analysis of immune-related AEs (Table 19). These are referred to in the CS as adverse events of special interest (AEOSI). The company found no difference in the frequency of AEOSIs between the pembrolizumab 2-weekly and 3-weekly dosing schedules in the broad categories of events and has therefore combined the AEOSI data for both of these trial arms.

The ERG notes that patients treated with pembrolizumab and patients treated with ipilimumab have similar rates of AEOSIs (18.4% vs 19.6%). However, the ERG also notes that treatment with pembrolizumab is associated with fewer grade 3 to 5 AEs and SAEs compared to treatment with ipilimumab.

Table 19 Adverse events of special interest (KEYNOTE-006)

Adverse event	**Ipilimumab 3mg/kg n=256**	**Pembrolizumab 10mg/kg Q2W+Q3W n=555**
	n (%)	n (%)
One or more AE	47 (18.4)	109 (19.6)
No AE	209 (81.6)	446 (80.4)
Drug-related† AE	43 (16.8)	94 (16.9)
Toxicity grade 3 to 5 AE	30 (11.7)	30 (5.4)
Toxicity grade 3 to 5 drug-related AE	29 (11.3)	24 (4.3)
Serious AE	27 (10.5)	28 (5.0)
Serious drug-related AE	26 (10.2)	25 (4.5)
Death	0 (0.0)	0 (0.0)
Death due to a drug-related AE	0 (0.0)	0 (0.0)
Discontinuation‡ due to AE	14 (5.5)	15 (2.7)
Discontinuation due to drug-related AE	13 (5.1)	15 (2.7)
Discontinuation due to serious AE	13 (5.1)	14 (2.5)
Discontinuation due to serious drug-related AE	12 (4.7)	14 (2.5)

AE=adverse event; Q2W=every 2 weeks; Q3W=every 3 weeks
† Determined by the investigator to be related to the drug
‡ Study medication withdrawn
Source: CS, Table 59

The numbers of patients experiencing specific AEOSIs are presented in Table 60 of the CS. The ERG notes that for any grade of AEOSI, treatment with pembrolizumab is associated with a higher frequency of hypothyroidism (8.7%) and hyperthyroidism (3.2%) than ipilimumab. In terms of grade 3 to 5 events experienced by patients receiving pembrolizumab, the most frequently occurring AEOSIs are colitis (2.5%) and hepatitis (1.8%).

For patients treated with ipilimumab, the most frequently reported AEOSIs of any grade are colitis (8.2%), hyperthyroidism (2.3%), hypophysitis (2.3%) and pneumonitis (1.8%). At grades 3 to 5, the most frequently occurring events for patients treated with ipilimumab are colitis (7.0%) and hypophysitis (1.6%).

Analyses of adverse events adjusted for differences in time on treatment

To take into account the differences in treatment duration between patients randomised to the ipilimumab arm and those randomised to either of the pembrolizumab arms (51 days versus 164 days), the company conducted three further analyses:

- AEs by time periods (weeks 0 to 6, weeks 7 to 12 and weeks 13 to 18)
- overall AEs by drug exposure (events/person year)
- overall grade 3 to 5 AEs (i.e. time to first event, to allow a direct comparison of the initial onset of toxicity for treatment with pembrolizumab versus treatment with ipilimumab).

The results of the company's analyses, adjusted for differences in time on treatment, are presented in the CS (Appendix 14). The ERG agrees with the company that the results demonstrate that in terms of the time of onset of AEs, the onset was earlier for patients treated with ipilimumab than it was for patients treated with pembrolizumab. Also, for patients treated with ipilimumab toxicities tended to occur at a higher rate per unit of time during time on treatment compared to patients treated with pembrolizumab.

In summary, the ERG considers that treatment with pembrolizumab was associated with a similar frequency of AEs when compared to treatment with ipilimumab (AEs of all grades and AEs of grade 3 and above). However, fewer patients treated with pembrolizumab experienced grade 3 to 5 drug-related AEs and SAEs when compared to patients treated with ipilimumab. For patients treated with pembrolizumab, the most frequently occurring AEOSIs at grades 3 to 5 are colitis and hepatitis. For patients treated with ipilimumab, the most frequently occurring AESOIs are colitis and hypophysitis.

4.8 Critique of the indirect evidence

This section provides a summary and critique of the indirect evidence provided by the company. The ERG notes that the results of the company's NMAs that are described

in the CS are not used in their base case cost effectiveness assessment. However, the results are used in scenario analyses only. Dacarbazine is included as a comparator in the NMAs. However, the company and the ERG do not consider dacarbazine as a relevant comparator to pembrolizumab.

4.9 Network meta-analysis: overview of trials and statistical approach

Six RCTs[22,25,28,36,43,44] were identified for inclusion in the company's NMAs. A search carried out by the ERG did not identify any additional trials that met the company's eligibility criteria. A summary of the key characteristics of the trials included in the NMAs is provided in Table 20.

Table 20 Summary of trials included in the NMAs

Trial	Intervention and comparator	Populations
KEYNOTE-006	Pembrolizumab 10mg/kg Q2W Pembrolizumab 10mg/kg Q3W Ipilimumab 3mg/kg Q3W	No restriction by $BRAF^{V600}$ mutation status 1st/2nd line patients
BREAK-3[25]	Dabrafenib 150mg bid Dacarbazine 1000 mg/m^2 Q3W	$BRAF^{V600}$ mutation positive patients only 1st line patients only (patients allowed prior treatment with IL-2 only)
BRIM-3[22,45]	Vemurafenib 960mg bid Dacarbazine 1000 mg/m^2 Q3W	$BRAF^{V600}$ mutation positive patients only 1st line patients only
Hersh 2011[43]	Ipilimumab 3mg/kg Q4W Dacarbazine 250 mg/m^2 5 days/3 weeks + ipilimumab 3mg/kg Q4W	No restriction by $BRAF^{V600}$ mutation status 1st/2nd line patients
Robert 2011[28]	Dacarbazine 850mg/m^2 Q3W+ipilimumab 10mg/kg weeks 1, 4, 7, and 10 Dacarbazine 850 mg/m^2 Q3W	No restriction by $BRAF^{V600}$ mutation status 1st line patients only
Hodi 2010[44]	Ipilimumab 3mg/kg Q3W + gp100 Q3W Ipilimumab 3mg/kg Q3W gp100 Q3W	No restriction by $BRAF^{V600}$ mutation status 2nd line patients only

IL-2=interleukin-2; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks

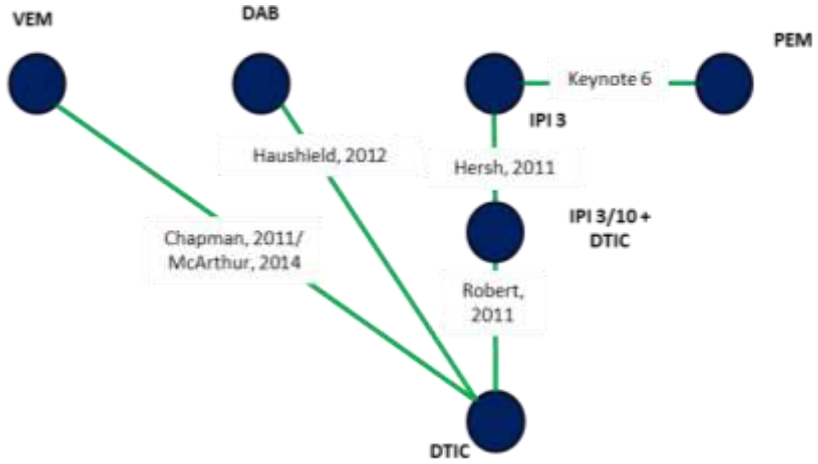
The investigators in the BREAK-3,[25] BRIM-3[22,45] and Hersh[43] trials allowed treatment switching. In the BREAK-3[25] trial, patients were permitted to crossover from the dacarbazine 1000 mg/m^2 Q3W arm to the dabrafenib 150mg twice daily arm on disease progression. Patients in the BRIM-3[22,45] trial were allowed to switch from dacarbazine 1000mg/m^2 Q3W to vemurafenib 960mg twice daily if recommended by the data safety monitoring board. On disease progression patients recruited to the Hersh[43] trial could switch from ipilimumab 3mg/kg Q4W to dacarbazine 250mg/m^2 for 5 days every 3 weeks then ipilimumab 3 mg/kg Q4W.

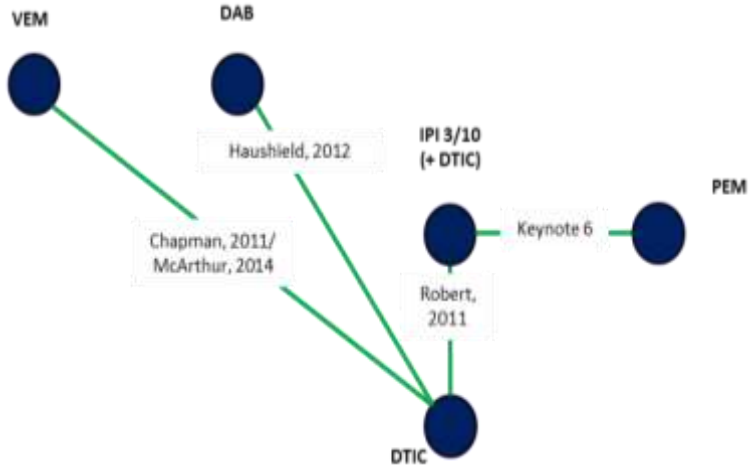
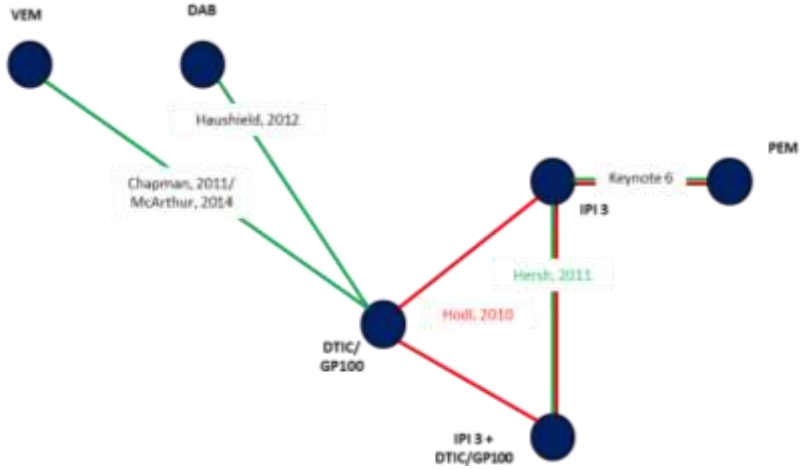
Networks of evidence

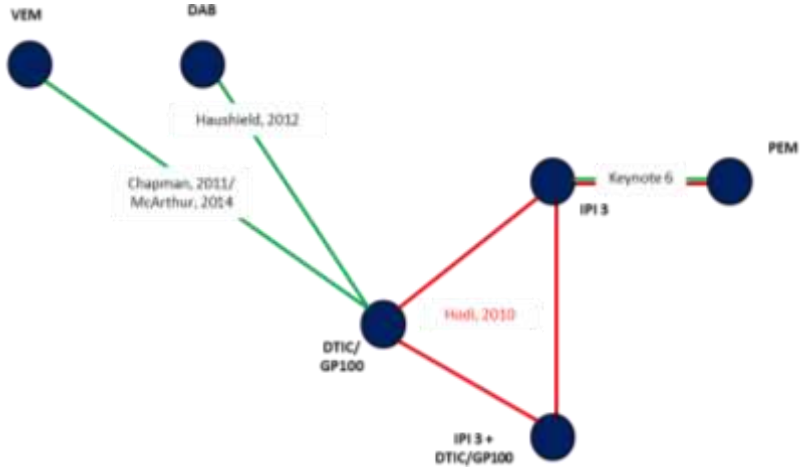
The company conducted NMAs using four different scenarios. Each scenario consisted of a different network structure. Within each network structure, different efficacy assumptions were used to connect trials within the network; different combinations of trials were included in each of the four scenarios. A network diagram for each of the scenarios, and the different assumptions employed to form each network, are provided in Table 21.

For two of the scenario networks, analyses could be performed for a wholly first-line patient population (scenarios 1 and 2 in Table 21). For the other two scenario networks, both first- and second-line patients are included in the analyses (scenarios 3a and 3b in Table 21).

Table 21 Overview of the NMA scenarios and their related assumptions and limitations

Scenario	Outcomes	Network of evidence	Assumptions / limitations
1 First-line treatment	PFS OS		The efficacy of ipilimumab 3mg/kg+dacarbazine is assumed to be similar to that of ipilimumab 10 mg/kg+dacarbazine The OS results from the Hersh[43] trial were affected by crossover PFS results were not reported for the Hersh[43] trial, therefore PFS was estimated using the OS and PFS HR relationship observed in by Flaherty[55] Patients in the Hersh[43] trial were chemotherapy naïve but 45.8% had previous immune therapy Crossover in the BREAK-3[25] trial affected OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty [55] The patients in the BREAK-3[25] trial were chemotherapy-naïve but 26.8% had previously received immune therapy The BRIM-3[22,45] trial allowed crossover: HRs, with and without crossover adjustment, were similar. As such, reported OS K-M curves without crossover adjustment were assumed to represent relative treatment effects without crossover

Scenario	Outcomes	Network of evidence	Assumptions / limitations
2 First-line treatment	PFS OS		The efficacy of ipilimumab 3 mg/kg+dacarbazine is assumed to be of similar to that of ipilimumab 10mg/kg+dacarbazine Crossover in the BREAK-3[25] trial affected OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty[55] In the BREAK-3[25] trial, patients were chemotherapy naïve but 26.8% had previous immune therapy The BRIM-3[22,45] trial allowed crossover: HRs, with and without crossover adjustment, were similar. As such, reported OS K-M curves without crossover adjustment were assumed to represent relative treatment effects without crossover
3a First- and second-line treatment Patients with BRAF wild -type mutations	OS		The efficacy of ipilimumab 3mg/kg+dacarbazine is assumed to be similar to that of ipilimumab 3mg/kg+gp100 Dacarbazine is assumed to be of similar efficacy to that of gp100 The OS results from the Hersh[43] trial were affected by crossover Crossover in the BREAK-3[25] trial affected OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty[55] The BRIM-3[22,45] trial allowed crossover: HRs, with and without crossover adjustment, were similar. As such, reported OS K-M curves without crossover adjustment were assumed to represent relative treatment effects without crossover Covariate in model to adjust for between-trial differences in proportion 2nd-line (i.e. proportion previous systemic treatment: KEYNOTE-006 1st-line covariate=0; KEYNOTE-006 1st-line covariate=1; Hodi[44] covariate=1; Hersh[43] covariate=0.458; BRIM-

Scenario	Outcomes	Network of evidence	Assumptions / limitations
			3[22,45] covariate=0; BREAK-3[25] covariate=0.268) The relative difference in relative treatment effects between first-line and second-line is the same for all interventions relative to IPI 3. The covariate estimate is treatment independent
3b First- and second-line treatment	PFS OS		The efficacy of ipilimumab 3mg/kg+dacarbazine is assumed to be similar to that of ipilimumab 3mg/kg+gp100 Dacarbazine is assumed to be of similar efficacy to that of gp100 Crossover in the BREAK-3[25] trial affected OS HRs; HR OS based on PFS data and relationship between HR PFS and HR OS based on Flaherty[55] The BRIM-3[22,45] trial allowed crossover: HRs, with and without crossover adjustment, were similar. As such, reported OS K-M curves without crossover adjustment were assumed to represent relative treatment effects without crossover Covariate in model to adjust for between-trial differences in proportion second-line (i.e. proportion previous systemic treatment: KEYNOTE-006 first-line covariate=0; KEYNOTE-006 first-line covariate=1; Hodi[44] covariate=1; Hersh[43] covariate=0.458; BRIM-3[22,45] covariate=0; BREAK-3[25] covariate=0.268) The relative difference in relative treatment effects between first-line and second-line is the same for all interventions relative to ipilimumab 3mg/kg. The covariate estimate is treatment independent.

DAB=dabrafenib; DTIC=dacarbazine; gp100=glycoprotein 100; HR=hazard ratio; ipi=ipilimumab; K-M=Kaplan-Meier; OS=overall survival; pem=pembrolizumab; PFS=progression-free survival; vem=vemurafenib
Green line=first-line patients. Red line=second-line patients
Source: CS, Table 41

4.9.1 Populations in the included trials

The company has provided results from the NMAs for the:

- first-line treatment for patients with $BRAF^{V600}$ positive mutations
- first-line treatment for patients with $BRAF^{V600}$ wild-type mutations and
- second-line treatment for patients with $BRAF^{V600}$ wild-type mutations.

Due to lack of available data, second-line treatment for patients with $BRAF^{V600}$ mutation positive melanoma was not considered.

Evidence is available for first-line treatment with pembrolizumab, ipilimumab, dacarbazine, vemurafenib and dabrafenib for patients with $BRAF^{V600}$ positive mutations. Evidence is available for first- and second-line treatment with pembrolizumab, ipilimumab, and dacarbazine for patients with $BRAF^{V600}$ wild-type mutations.

The ERG notes that since the introduction of ipilimumab into clinical practice in England and Wales, dacarbazine is now rarely used as a treatment for metastatic melanoma. As noted in Section 2 of this ERG report, dacarbazine is considered to be of little clinical benefit and may be included as part of a BSC treatment package.

4.9.2 Network meta-analysis methodology

NMAs were undertaken for each scenario to provide results for both PFS and OS, with the exception that only OS results were generated for scenario 3a. The ERG considers that this exception may be due to the fact that the published paper describing the Hersh[43] trial does not include PFS curves. The ERG notes that for scenario 1, PFS data from the Hersh[43] trial were generated using OS data, and that the relationship between PFS and OS is described by Flaherty[55] (and discussed in the next sub-section, entitled '*Assumptions and limitations*'). The ERG asked the company for clarification as to why this method was not used to provide PFS results for scenario 3a. The company responded that data from the Hersh[43] trial were required to form a connection between dacarbazine and ipilimumab for scenario 1, and without this data a network of evidence for PFS would not be formed. However, for scenario 3a, data from the Hersh[43] trial were not required to form a network of evidence for PFS so it was possible to generate PFS results without imputing data for the Hersh[43] trial. Without the Hersh[43] trial, scenario 3a and scenario 3b are the same.

Hence, no results were reported for PFS under scenario 3a. The ERG is satisfied with the company's rationale for this decision.

The company explains that instead of undertaking the NMAs using methods that rely on the proportional hazards assumption (which is often violated or implausible) a multivariate treatment effect measure was used as this method describes how the hazard ratio develops over time. The company refers to a paper by Jansen,[56] which describes a NMA method using fractional polynomials, which model hazard rates with a two dimensional treatment effect. The company then implemented the Weibull model to estimate relative treatment effects between interventions. This fractional polynomial method allows the incorporation of curves that describe PFS and OS over time into the NMAs.

Each NMA was undertaken in the Bayesian framework. The company used OpenBUGS to implement the Markov Chain Monte Carlo (MCMC) method to provide estimates of the model parameters.

For the scenario networks that include first- and second-line patients (scenarios 3a and 3b) meta-regression analysis was used to adjust for differences in patient characteristics among first- and second-line patients.

Assumptions and limitations

The company made several assumptions in order allow the NMAs for each of the scenario networks outlined in Table 21:

- $BRAF^{V600}$ mutation status is not a significant effect-modifier for all treatments not specifically targeting BRAF
- Several treatments were assumed to be of similar efficacy, as described in Table 21
- BRIM-3[22,45] trial: the unadjusted K-M curve would be representative of a K-M curve adjusted for crossover
- BREAK-3[25] trial: the log hazard ratios over time between dabrafenib and dacarbazine are similar for PFS and OS with respect to their shape parameters, and only differ regarding scale. The BREAK-3[25] trial had crossover affecting OS HRs; the PFS-OS relationship described by Flaherty[55] could be used to obtain time-varying log hazard ratio for OS as if no crossover had occurred
- Hersh[43] trial: the PFS-OS relationship described by Flaherty[55] could be used to obtain time-varying log hazard ratio for PFS. Unadjusted data are used in the NMAs

- The meta-regression analyses: the impact of a covariate on relative treatment effects was the same for all interventions in the network.

The company also assumed that the efficacy of treatment with pembrolizumab 10mg/kg Q3W was equivalent to treatment with pembrolizumab 2mg/kg Q3W (the anticipated licensed dose of pembrolizumab). The ERG notes that the EMA considers that the efficacy of the two doses is equivalent. The ERG has discussed this issue in detail within this ERG report (Sections 3 and 4.3.1).

4.9.3 Patient population characteristics of the included trials

A summary of the baseline characteristics of patients recruited to the trials included in the NMAs is presented in Table 22.

Table 22 Summary of the baseline characteristics of patients recruited to the trials included in the network meta-analyses

Trial	Treatment	Age, median (range)	Males n (%)	White n (%)	ECOG score n (%)		Melanoma stage n (%)					LDH > ULN n (%)	Brain metastasis n (%)	Any BRAF mutation n (%)
					0	1	IIIU	M0	M1a	M1b	M1c			
KEYNOTE-006	Pembrolizumab 10mg/kg Q2W	61 (18-89)	161 (58)	273 (98)	196 (70)	83 (30)	NR	9 (3)	21 (8)	64 (23)	179 (64)	81 (29)	23 (8)	98 (35)
	Pembrolizumab 10mg/kg Q3W	63 (22-89)	174 (63)	271 (98)	189 (68)	88 (32)	NR	9 (3)	34 (12)	41 (15)	189 (68)	98 (35)	27 (10)	97 (35)
	Ipilimumab 3mg/kg Q3W	62 (18-88)	162 (50)	272 (98)	188 (68)	90 (32)	NR	14 (5)	30 (11)	52 (19)	177 (64)	91 (33)	28 (10)	107 (39)
BREAK-3[25]	Dabrafenib 150mg bid	53 (22-93)	112 (60)	187 (100)	124 (66)	NR	NR	6 (3)	23 (12)	34 (18)	124 (66)	67 (36)	0	187 (100)
	Dacarbazine 1000mg/m^2 Q3W	50 (21-82)	37 (59)	63 (100)	44 (70)	NR	NR	1 (2)	10 (16)	12 (19)	40 (63)	19 (30)	0	63 (100)
BRIM-3[22,45]	Vemurafenib 960mg bid	56 (21-86)	200 (50)	333 (99)	229 (68)	108 (32)	20 (6)	NR	34 (10)	62 (18)	221 (66)	195 (58)	0	337 (100)
	Dacarbazine 1000mg/m^2 Q3W	52 (17-86)	181 (54)	338 (100)	230 (68)	108 (32)	13 (4)	NR	40 (12)	65 (19)	220 (65)	196 (58)	0	338 (100)
Hersh 2011[43]	Ipilimumab 3mg/kg Q4W	66 (25-82)	21 (57)	34 (92)	NR	NR	NR	NR	8 (22)	8 (22)	21 (57)	10 (27)	NR	NR
	Dacarbazine 250mg/m^2 5 days/3 weeks +ipilimumab 3mg/kg Q4W	60 (27-82)	26 (70)	31 (89)	NR	NR	NR	NR	6 (17)	12 (34)	16 (46)	8 (23)	NR	NR
Robert	Dacarbazine	57.5*	152	NR	177	73	NR	6 (2)	37	64	143	93 (37)	0	NR

Trial	Treatment	Age, median (range)	Males n (%)	White n (%)	ECOG score n (%)		Melanoma stage n (%)					LDH > ULN n (%)	Brain metastasis n (%)	Any BRAF mutation n (%)
					0	1	IIIU	M0	M1a	M1b	M1c			
2011[28]	850mg/m^2 Q3W+ ipilimumab 10 mg/kg weeks 1, 4, 7, and 10		(61)		(71)	(29)			(15)	(26)	(57)			
	Dacarbazine 850mg/m^2 Q3W	56.4*	149 (59)	NR	179 (71)	73 (29)	NR	8 (3)	43 (17)	62 (25)	139 (55)	110 (44)	0	NR
Hodi 2010[44]	Ipilimumab 3mg/kg Q3W+gp100 Q3W	55.6*	247 (60)	380 (94)	232 (58)	166 (41)	NR	NR	37 (9)	76 (19)	285 (71)	149 (37)	46 (11)	NR
	Ipilimumab 3mg/kg Q3W	56.8*	81 (59)	129 (94)	72 (53)	64 (47)	NR	NR	14 (10)	22 (16)	100 (73)	53 (39)	15 (11)	NR
	gp100 Q3W	57.4*	73 (54)	129 (95)	70 (52)	61 (45)	NR	NR	11 (8)	23 (17)	98 (72)	52 (38)	21 (15)	NR

Bid=twice daily; ECOG=Eastern Cooperative Oncology Group; gp100=glycoprotein 100; LDH=lactate dehydrogenase; NR=not reported; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; U=unresectable; ULN=upper limit of normal

*The ERG assumes that these are mean ages rather than median ages, but this is not clear in the CS

Source: CS Appendix 8 Table 6

The company states that the baseline characteristics of patients (including age, proportion of males, proportion of Caucasian patients, and proportion of patients with an ECOG score of 0) were comparable across the included studies. The ERG has concerns about the comparability of the patient populations in the control arms of the included trials, and these concerns are discussed in detail in Section 4.10.3.

The company provides a summary table (CS Appendix 8 [Table 2]) of previous systemic treatment experience among patients in the included trials. The patients included in the BRIM-3[22,45] and Robert[28] trials had not had any prior systemic treatment. Patients included in the BREAK-3[25] and the Hersh[43] trials were allowed to have received previous immunotherapy, but not chemotherapy. Patients in the KEYNOTE-006 and Hodi[44] trials were allowed to have had any type of previous systemic treatment.

4.9.4 Quality assessment

In Appendix 8 of the CS, the company presents a summary of its risk of bias assessment for each of the trials included in the NMAs. The company's risk of bias assessment is based on the criteria recommended by NICE for company submissions[49] and uses the Cochrane Collaboration's guidelines[57] as the reference for judging risk. The company does not use the standard scoring system of the Cochrane tool[57] (high, low or unclear risk) but instead provides 'yes', 'no' or 'unclear' as possible responses for each criterion.

The company's risk of bias assessment results and the ERG's critique of the assessment are similar. The ERG considers the majority of trials to be at an overall low risk of bias.

4.9.5 Individual trial findings

The company provides results from the individual trials included in the NMAs in Appendix 11 of the CS.

4.10 Results of the network meta-analysis

The company provides results for first- and second-line patients separately, for both OS and PFS. For each set of results, hazard ratios are provided at different time points for the comparison of pembrolizumab relative to other treatments, and also for the comparison of ipilimumab to other treatments. The ERG has reproduced the tables in the CS that provide hazard ratios for pembrolizumab relative to other treatments as these results are of direct relevance to the decision problem.

4.10.1 First-line population

Progression-free survival

The PFS results from the NMAs for the first-line population are provided in Table 23 (pembrolizumab treatment effect relative to other treatments) and Table 24 (treatment effects relative to ipilimumab).

Pembrolizumab was found to statistically significantly improve PFS in comparison to ipilimumab at 3, 6 and 12 months, for all scenarios. When compared with dacarbazine, pembrolizumab was also shown to statistically significantly improve PFS at all time-points, in all scenarios except scenario 1. There was some evidence that pembrolizumab may improve PFS in comparison to vemurafenib for the $BRAF^{V600}$ mutation positive population, as suggested by statistically significant differences at 6 and 12 months for scenario 2, and at 12 months only for scenario 3b. No statistically significant differences were observed between pembrolizumab and dabrafenib in terms of PFS for the $BRAF^{V600}$ mutation positive population.

Table 23 Results of NMAs: first-line treatment, PFS. Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments

		Hazard ratio with pembrolizumab relative to other treatments								
		Scenario 1			Scenario 2			Scenario 3b		
Reference treatment*	**Time point (months)**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**
Ipilimumab*	3	0.51	0.39	0.66	0.50	0.38	0.66	0.50	0.38	0.65
	6	0.46	0.32	0.64	0.45	0.32	0.64	0.45	0.33	0.62
	12	0.41	0.24	0.71	0.41	0.23	0.71	0.41	0.26	0.64
Dacarbazine*	3	0.70	0.21	2.58	0.43	0.30	0.60	0.54	0.33	0.82
	6	0.50	0.17	1.46	0.34	0.22	0.50	0.36	0.21	0.59
	12	0.36	0.12	1.00	0.27	0.14	0.49	0.24	0.12	0.48
Vemurafenib**	3	1.88	0.54	7.09	1.15	0.77	1.72	1.46	0.84	2.35
	6	0.93	0.32	2.78	0.63	0.39	0.97	0.67	0.37	1.14
	12	0.46	0.14	1.36	0.34	0.17	0.68	0.31	0.15	0.65
Dabrafenib**	3	2.27	0.60	9.28	1.40	0.80	2.42	1.76	0.88	3.26
	6	1.11	0.29	4.04	0.75	0.33	1.71	0.80	0.32	1.92
	12	0.55	0.09	2.71	0.40	0.11	1.49	0.36	0.09	1.44

CrI=credible interval; HR=hazard ratio
*Applicable to both patients with BRAF wild-type mutations and those with BRAF positive mutations
**Applicable to patients with BRAF positive mutations
Source: CS, Table 44

Table 24 Results of NMAs: first-line treatment, PFS. Treatment effects as hazard ratio at different time points relative to ipilimumab

		Hazard ratio relative to ipilimumab								
		Scenario 1			Scenario 2			Scenario 3b		
Treatment	**Time point (months)**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**
Dacarbazine*	3	0.72	0.20	2.41	1.18	0.95	1.47	0.91	0.56	1.70
	6	0.91	0.33	2.47	1.34	1.09	1.65	1.23	0.75	2.22
	12	1.13	0.47	2.93	1.53	1.13	2.08	1.67	0.93	3.15
Pembrolizumab*	3	0.51	0.39	0.66	0.50	0.38	0.66	0.50	0.38	0.65
	6	0.46	0.32	0.64	0.45	0.32	0.64	0.45	0.33	0.62
	12	0.41	0.24	0.71	0.41	0.23	0.71	0.41	0.26	0.64
Vemurafenib**	3	0.27	0.07	0.91	0.44	0.33	0.59	0.34	0.20	0.66
	6	0.49	0.17	1.37	0.72	0.54	0.98	0.66	0.38	1.27
	12	0.88	0.34	2.50	1.19	0.77	1.85	1.32	0.67	2.68
Dabrafenib**	3	0.22	0.06	0.81	0.36	0.22	0.59	0.28	0.15	0.59
	6	0.41	0.12	1.49	0.60	0.29	1.28	0.55	0.23	1.41
	12	0.74	0.17	3.96	1.01	0.31	3.34	1.12	0.30	4.28

CrI=credible interval; HR=hazard ratio
*Applicable to both patients with BRAF wild-type mutations and those with BRAF positive mutations
**Applicable to the BRAF mutation positive population
Source: CS, Table 45

Overall survival

The NMA OS results for the first-line population are provided in Table 25 (pembrolizumab treatment effect relative to other treatments) and Table 26 (treatment effects relative to ipilimumab).

Pembrolizumab was found to statistically significantly improve OS in comparison to ipilimumab at 6 and 12 months, for all scenario analyses. This beneficial effect was not statistically significant at 18 months, with the exception of scenario 3a. Pembrolizumab was also shown to be statistically significantly better than dacarbazine for all time-points, with the exception of scenario 1, and statistically significantly better than vemurafenib for the $BRAF^{V600}$ mutation positive population at 12 and 18 months for all scenario analyses, and at 6 months only for scenario 2. No statistically significant differences were observed between pembrolizumab and dabrafenib for the $BRAF^{V600}$ mutation positive population.

Table 25 Results of NMAs: first-line treatment, OS. Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments

		Hazard ratio with pembolizumab relative to other treatments											
		Scenario 1			Scenario 2			Scenario 3a			Scenario 3b		
Reference treatment	**Time point (months)**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**
Ipilimumab*	6	0.59	0.42	0.83	0.59	0.42	0.84	0.57	0.42	0.79	0.59	0.41	0.84
	12	0.59	0.38	0.92	0.59	0.38	0.93	0.59	0.40	0.87	0.61	0.39	0.93
	18	0.59	0.34	1.04	0.60	0.34	1.05	0.60	0.38	0.97	0.62	0.37	1.04
Dacarbazine*	6	0.65	0.25	1.92	0.45	0.30	0.67	0.58	0.37	0.88	0.54	0.30	0.91
	12	0.55	0.28	1.00	0.43	0.26	0.71	0.49	0.30	0.79	0.44	0.24	0.81
	18	0.51	0.23	1.09	0.42	0.23	0.79	0.45	0.24	0.80	0.40	0.20	0.81
Vemurafenib**	6	0.82	0.41	1.70	0.63	0.39	0.99	0.80	0.49	1.28	0.75	0.40	1.34
	12	0.48	0.23	0.92	0.38	0.21	0.67	0.43	0.24	0.75	0.39	0.20	0.74
	18	0.35	0.14	0.78	0.28	0.14	0.58	0.30	0.15	0.59	0.26	0.12	0.57
Dabrafenib**	6	1.06	0.46	2.45	0.80	0.43	1.51	1.05	0.53	1.95	0.96	0.46	1.93
	12	0.77	0.27	2.01	0.62	0.25	1.54	0.71	0.28	1.69	0.63	0.23	1.67
	18	0.64	0.18	2.07	0.53	0.17	1.64	0.57	0.18	1.66	0.49	0.15	1.59

CrI=credible interval; HR=hazard ratio
*Applicable to both patients with BRAF wild-type mutations and those with BRAF positive mutations
**Applicable to the BRAF mutation positive population
Source: CS, Table 42

Table 26 Results of NMAs; first-line treatment, OS. Treatment effects as hazard ratio at different time points relative to ipilimumab

		Hazard ratio relative to ipilimumab											
		Scenario 1			Scenario 2			Scenario 3a			Scenario 3b		
Treatment	**Time point (months)**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**
Dacarbazine*	6	1.01	0.52	1.78	1.32	1.08	1.63	0.99	0.64	1.60	1.08	0.57	2.19
	12	1.08	0.71	1.84	1.38	1.14	1.70	1.21	0.77	1.92	1.36	0.70	2.77
	18	1.13	0.71	2.07	1.41	1.12	1.81	1.37	0.83	2.21	1.55	0.77	3.25
Pembrolizumab*	6	0.59	0.42	0.83	0.59	0.42	0.84	0.57	0.42	0.79	0.59	0.41	0.84
	12	0.59	0.38	0.92	0.59	0.38	0.93	0.59	0.40	0.87	0.61	0.39	0.93
	18	0.59	0.34	1.04	0.60	0.34	1.05	0.60	0.38	0.97	0.62	0.37	1.04
Vemurafenib**	6	0.72	0.37	1.32	0.95	0.70	1.29	0.71	0.43	1.20	0.77	0.40	1.66
	12	1.23	0.76	2.25	1.57	1.12	2.22	1.38	0.81	2.34	1.55	0.78	3.30
	18	1.69	0.96	3.48	2.11	1.38	3.24	2.03	1.11	3.65	2.32	1.09	5.14
Dabrafenib**	6	0.56	0.25	1.19	0.74	0.44	1.24	0.55	0.30	1.07	0.61	0.28	1.46
	12	0.76	0.32	1.97	0.97	0.45	2.12	0.84	0.35	2.01	0.96	0.35	2.76
	18	0.92	0.32	2.91	1.14	0.43	2.98	1.07	0.38	3.10	1.26	0.38	4.22

CrI=credible interval; HR=hazard ratio
*Applicable to both patients with BRAF wild-type mutations and those with BRAF positive mutations
**Applicable to the BRAF mutation positive population
Source: CS, Table 43

4.10.2 Second-line population

Progression-free survival

The PFS results from the NMAs for the second-line population are presented in Table 27 and Table 28. In the two scenarios treatment with pembrolizumab is shown to statistically significantly improve PFS when compared to dacarbazine at 6, 12 and 18 months. No statistically significant differences were observed when treatment with pembrolizumab is compared with treatment with ipilimumab.

Table 27 Results of NMA: second-line treatment, PFS. Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments

		Hazard ratio with pembrolizumab relative to other treatments		
		Scenario 3b		
Reference treatment	**Time point (months)**	**HR**	**95% CrI low**	**95% CrI high**
Ipilimumab*	3	0.81	0.58	1.15
	6	0.74	0.48	1.12
	12	0.67	0.38	1.16
Dacarbazine*	3	0.51	0.33	0.80
	6	0.34	0.21	0.56
	12	0.23	0.12	0.45

CrI=credible interval; HR=hazard ratio
*Applicable to the BRAF wild- type population
Source: CS, Table 48

Table 28 Results of NMA: second-line treatment, PFS. Treatment effects as hazard ratio at different time points relative to ipilimumab

		Hazard ratio relative to ipilimumab		
		Scenario 3b		
Treatment	**Time point (months)**	**HR**	**95% CrI low**	**95% CrI high**
Dacarbazine*	3	1.59	1.22	2.06
	6	2.15	1.62	2.83
	12	2.91	1.94	4.36
Pembrolizumab*	3	0.81	0.58	1.15
	6	0.74	0.48	1.12
	12	0.67	0.38	1.16

CrI=credible interval; HR=hazard ratio
*Applicable to the BRAF wild- type population
Source: CS, Table 49

Overall survival

The results from the OS NMA for the second-line population are presented in Table 29 and Table 30. Pembrolizumab was found to statistically significantly improve OS in comparison to dacarbazine at 6, 12 and 18 months for both of the scenario analyses that provided results for this patient population. No statistically significant differences were observed between pembrolizumab and ipilimumab in terms of OS.

Table 29 Results of NMAs: second-line treatment, OS. Treatment effects as hazard ratio at different time points with pembrolizumab relative to other treatments

		Hazard ratio with pembrolizumab relative to other treatments					
		Scenario 3a			Scenario 3b		
Reference treatment	**Time point (months)**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**
Ipilimumab*	6	0.84	0.55	1.26	0.80	0.52	1.22
	12	0.87	0.54	1.40	0.83	0.51	1.36
	18	0.89	0.51	1.55	0.84	0.48	1.51
Dacarbazine*	6	0.57	0.35	0.93	0.53	0.32	0.88
	12	0.48	0.29	0.84	0.44	0.25	0.80
	18	0.44	0.24	0.84	0.40	0.20	0.78

CrI=credible interval; HR=hazard ratio
*Applicable to patients with BRAF wild-type mutations
Source: CS, Table 46

Table 30 Results of NMAs: second-line treatment, OS. Treatment effects as hazard ratio at different time points relative to ipilimumab

		Hazard ratio relative to ipilimumab					
		Scenario 3a			Scenario 3b		
Treatment	**Time point (months)**	**HR**	**95% CrI low**	**95% CrI high**	**HR**	**95% CrI low**	**95% CrI high**
Dacarbazine*	6	1.47	1.13	1.91	1.50	1.15	1.96
	12	1.79	1.34	2.37	1.86	1.40	2.50
	18	2.02	1.42	2.80	2.11	1.49	3.03
Pembrolizumab*	6	0.84	0.55	1.26	0.80	0.52	1.22
	12	0.87	0.54	1.40	0.83	0.51	1.36
	18	0.89	0.51	1.55	0.84	0.48	1.51

CrI=credible interval; HR=hazard ratio
*Applicable to patients with BRAF wild-type mutations
Source: CS, Table 47

4.10.3 ERG critique of the network meta-analyses

Assumptions

Clinical advice to the ERG is that the following assumptions of clinical equivalence are reasonable:

- Efficacy of ipilimumab 3mg/kg+dacarbazine can be assumed to be similar to that of ipilimumab 10mg/kg+dacarbazine (scenario 1)
- Efficacy of ipilimumab 3mg/kg can be assumed to be similar to that of ipilimumab 10mg/kg+dacarbazine (scenario 2)
- Efficacy of ipilimumab 3mg/kg+dacarbazine can be assumed to be similar to that of ipilimumab 3mg/kg+gp100 (scenario 3a and 3b)
- Efficacy of dacarbazine can be assumed to be similar to that of gp100 (scenario 3a and 3b).

For the scenario networks in which both first- and second-line patients are included (scenarios 3a and 3b), meta-regression analysis was used to adjust for differences in patient characteristics among first- and second-line patients. To undertake this analysis the company assumed that, for all interventions in the network, the impact of receiving a treatment was the same irrespective of whether it was delivered as first- or second-line treatment. Clinical advice to the ERG is that this assumption is also reasonable.

Clinical advice to the ERG also confirmed that the assumption that '$BRAF^{V600}$ mutation status is not a significant effect-modifier for all treatments that do not specifically target BRAF' is reasonable. The ERG notes that for the comparisons of pembrolizumab with vemurafenib and dabrafenib, results for a mixed patient population were incorporated from KEYNOTE-006, whereas all patients in the BREAK-3[25] and BRIM-3[22,45] had $BRAF^{V600}$ positive mutations. As the ERG considers that the assumption that '$BRAF^{V600}$ mutation status is not a significant effect-modifier' is reasonable, this comparison of different patient populations within the NMAs is not concerning.

Heterogeneity between included trials

The ERG has concerns about the comparability of the patient populations in the control arms of the included trials when estimating treatment effectiveness between pembrolizumab and vemurafenib or dabrafenib. Specifically, the ERG notes that a higher percentage of patients in the gp100 arm of the Hodi[44] trial had an ECOG score greater than or equal to 1 (49%), in comparison to the patients in the dacarbazine arms of BREAK-3[25] (25%) and BRIM-3[22,45] (32%). Patients in the gp100 arm of the Hodi[44] trial were also older (mean age 57.4) than patients in the dacarbazine arms of BREAK-3[25] (mean age 50) and BRIM-3[22,45] (mean age 52). These differences mean that patients are likely to be younger and fitter in the control

arms of the BREAK-3[25] and BRIM-3[22,45] trials than patients in the control arm of the Hodi[44] trial. Considerable differences were also observed with regards to the proportions of males, M1c stage patients, and elevated LDH levels. The ERG has summarised these important differences in Table 31.

Table 31 Patient characteristics in the control arms of the Hodi, BRIM-3 and BREAK-3 trials

Characteristic	Trial (arm)		
	Hodi[44] (gp100)	BRIM-3[22] (dacarbazine)	BREAK-3[22,25] (dacarbazine)
Age (mean)	57.4	52	50
Males	54%	54%	63%
ECOG score of 1 or more	49%	32%	25%
M1c stage	73%	65%	63%
LDH>ULN	38%	58%	30%

ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; ULN=upper limit of normal

In view of the extensive heterogeneity within this body of evidence, the ERG does not consider that any reliable estimates of survival effectiveness are possible between pembrolizumab and either vemurafenib

Methodology

In order to implement the results of NMA in the context of non-proportional hazards, the company has applied a complex analytical method (fractional polynomial modelling of hazard ratios) aimed at better reflecting variations in hazard ratios over time in the component trials of the evidence network. The true test of the appropriateness of applying such a technique to the evidence available for this appraisal is to compare the estimated hazard ratios with those available directly from the trials.

Figure 2 indicates that the fractional polynomial method fails to reflect the wide variations in the hazard ratio of pembrolizumab vs ipilimumab seen in the KEYNOTE-006 trial, and results in a trend close to a constant non-varying level (CS, Table 42 Scenario 3b). In particular, the estimated hazard ratio at the end of the observation period is clearly below the hazard ratio actually occurring in the trial. If these values are used to populate the long-term phase of the decision model the result is likely to be a much greater long-term survival advantage for pembrolizumab versus ipilimumab than is consistent with the available evidence from the KEYNOTE-006 trial giving the only direct evidence for these two agents. This leads the ERG to conclude that the NMA results based on the fractional polynomial method cannot be considered a reliable method for estimating the long-term relative

effectiveness for pembrolizumab versus ipilimumab, and hence for either of the other comparators in the evidence network.

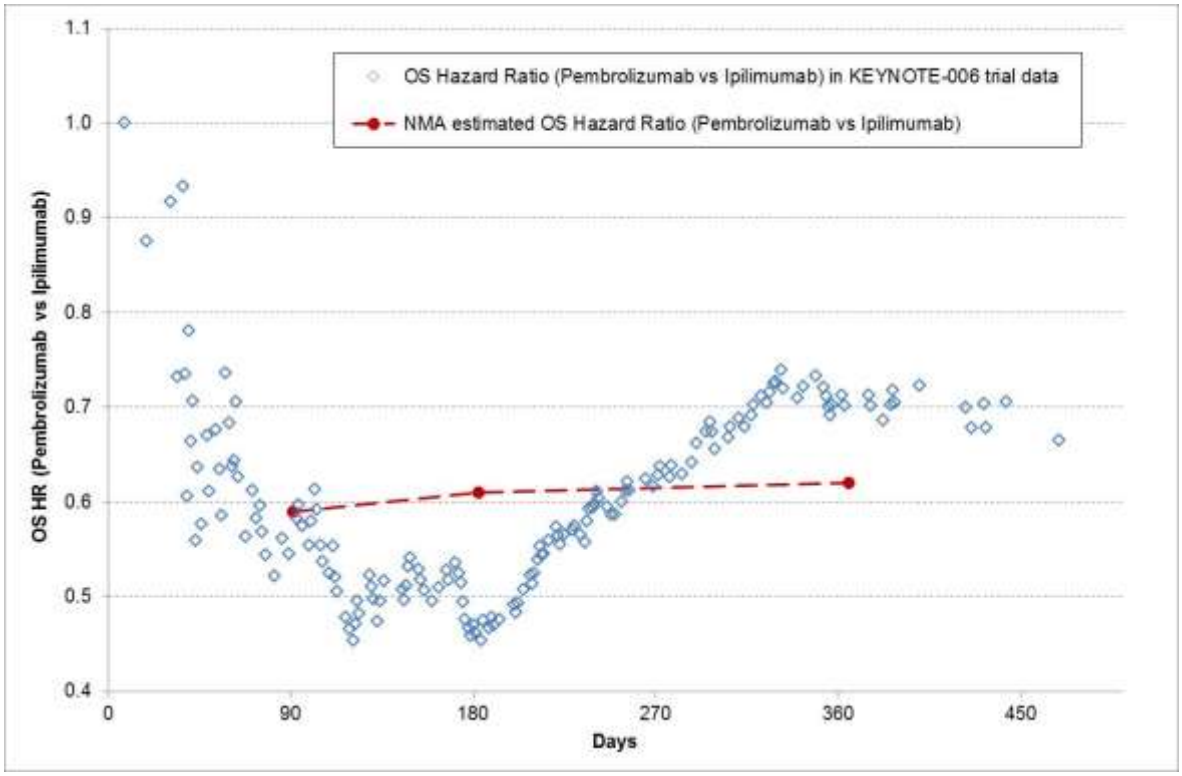


Figure 2 Comparison of HRs estimated directly from KEYNOTE-006 trial data, with estimated HRs obtained by fractional polynomial modelling of the NMA evidence net used in scenario 3a

Treatment switching

Patients in the BREAK-3,[25] BRIM-3[22,45] and Hersh[43] trials were allowed to switch treatments. The company employed various methods to analyse the survival data from these trials before the data were included in the NMAs. For data from the BREAK-3[25] trial, the company used the PFS-OS relationship described by Flaherty[55] to obtain time-varying log hazard ratios for OS as if no crossover had occurred. The ERG considers that this is an appropriate method of analysis and concludes that the company did everything possible to ensure a realistic estimate of OS for the dacarbazine arm of the BREAK-3[25] trial was incorporated in the NMAs. For data from the Hersh[43] trial, there were no crossover-adjusted curves available and therefore unadjusted data were used in the NMAs. The company highlights that the results from scenarios 2 and 3b are likely to be the most trustworthy as they do not include data from the Hersh[43] trial. The ERG agrees that results from scenario networks 1 and 3a should be interpreted with caution as they do include data from the Hersh[43] trial.

For data from the BRIM-3[22,45] trial, the hazard ratio for OS, unadjusted for crossover, was similar to the hazard ratio for adjusted OS (using rank-preserving structural failure time [RPSFT] methodology). Therefore, the company assumed that the unadjusted K-M curve would be representative of a K-M curve adjusted for crossover, and incorporated the unadjusted K-M curve into the analyses. The ERG considers that, as the adjusted hazard ratio was so similar to the unadjusted rate, the RPSFT method may not have adequately adjusted for crossover. The RPSFT method relies on the assumption of a "common treatment effect", which in practice is often an unrealistic assumption. The ERG is concerned that if an adequate adjustment has not been made to take account of the crossover effect, the treatment effect of vemurafenib in comparison to dacarbazine may be underestimated. As the NMAs compared the treatment effect of pembrolizumab versus dacarbazine to vemurafenib versus dacarbazine, the treatment effect of pembrolizumab in comparison to vemurafenib may consequently be overestimated. The ERG is of the opinion that comparisons made between pembrolizumab and vemurafenib using the results from the NMAs should be interpreted with caution.

ERG interpretation of network meta-analysis findings

Although the ERG believes that the methodology used to conduct the NMAs is flawed, the ERG agrees with the company that of the presented NMAs, scenarios 2 and 3b are the most reliable. The results from these two scenarios are summarised in Table 32. For the first-line population, where results are available for both scenarios 2 and 3b, results from the two networks are generally consistent. For the second-line population, the ERG only considers scenario 3b as results from scenario 2 are unavailable.

Table 32 Scenarios 2 and 3b from the company's NMAs

Population	Outcome	ERG conclusions
First-line	OS	**All patients** Pembrolizumab is statistically significantly better than ipilimumab at 6 and 12 months, but not at 18 months Pembrolizumab is statistically significantly better than dacarbazine at all time-points)
		BRAF mutation positive patients Pembrolizumab is statistically significantly better than vemurafenib (at all time-points for scenario 2, and at 12 and 18 months for scenario 3b); these findings should be interpreted with caution No statistically significant difference was detected between pembrolizumab and dabrafenib
	PFS	**All patients** Pembrolizumab is statistically significantly better than ipilimumab and dacarbazine at all time-points **BRAF mutation positive patients** Pembrolizumab is statistically significantly better than vemurafenib (at 6 and 12 month time points for scenario 2, and at 12 months only for scenario 3b); these findings should be interpreted with caution No statistically significant difference was detected between pembrolizumab and dabrafenib No statistically significant difference was detected between pembrolizumab and dabrafenib
Second-line	OS	**All patients** Pembrolizumab is statistically significantly better than dacarbazine at all time-points No statistically significant difference was detected between pembrolizumab and ipilimumab
	PFS	**All patients** Pembrolizumab is statistically significantly better than dacarbazine at all time-points No statistically significant difference was detected between pembrolizumab and ipilimumab

To conclude, the ERG has outlined several key concerns regarding the NMAs conducted by the company, and has reason to believe that the results of the NMAs cannot provide valid treatment effect estimates for pembrolizumab versus the relevant comparators. However, the ERG notes that the results of the NMAs are only used to inform the cost effectiveness of pembrolizumab in some of the scenario analyses and not in the base case comparisons. Therefore, the limitations of the NMA methodology do not have a major impact on the quality of evidence provided in the CS

4.11 Adverse events from the company network meta-analysis

The company presents the AE data that were extracted from the trials that were included in the company NMAs (CS, Appendix 8). The company's tables are reproduced in Appendix 2 of this ERG report.

The ERG considers that it is difficult to draw any overall conclusions regarding the safety of treatments included in the NMA and from the data available. The ERG notes that treatment

with pembrolizumab and ipilimumab are associated with relatively high frequencies of AEs of any kind (73% to 99%). Treatment with dabrafenib and dacarbazine appear to be associated with lower frequencies of any AE (54% and 44%). Where data are available, these show that the proportions of patients experiencing any AE at grade 3 and above ranged from 13% (ipilimumab) to 56% (dacarbazine plus ipilimumab). The majority of trials reported relatively few patients who discontinued treatment due to AEs; however, it is notable that 39% of patients treated with dacarbazine plus ipilimumab in the Robert[28] trial discontinued treatment due to AEs. Discontinuations due to disease progression or death ranged between 0% (pembrolizumab, ipilimumab, vemurafenib and dacarbazine) and 77% (dacarbazine).

With reference to treatment emergent AEs, the ERG considers that there are few data available to make any reliable comparisons across treatments. However, the ERG notes that for the outcome of any AE related to the skin, treatment with ipilimumab appears to be associated with relatively high frequencies in all trials in which ipilimumab was an intervention (40% to 49%). The exception is the KEYNOTE-006 trial in which less than 1% of patients treated with ipilimumab experienced a skin-related AE. The ERG further notes that none of the patients in either arm of the KEYNOTE-006 trial experienced any grade 3 to 5 immune-related AEs compared with 42% of patients treated with dacarbazine and ipilimumab in the publication by Robert 2011.[28]

4.12 Conclusions of the clinical effectiveness section

The clinical effectiveness evidence presented in the CS meets the criteria specified in the final scope issued by NICE.[32]

Direct evidence: pembrolizumab vs ipilimumab

- The key source of evidence used by the company to demonstrate the clinical effectiveness of pembrolizumab 2mg/kg Q3W when used to treat advanced melanoma in patients previously untreated with ipilimumab in a first- or second- line setting is the KEYNOTE-006 trial. Pembrolizumab can be used to treat patients with $BRAF^{V600}$ wild-type mutations as well as those with $BRAF^{V600}$ positive mutations

- The KEYNOTE-006 trial does not include a 2mg/kg Q3W arm. The company therefore assumes that pembrolizumab 2mg/kg Q3W and pembrolizumab 10mg/kg Q3W are clinically equivalent

- Results from the KEYNOTE-006 trial show that, compared to treatment with ipilimumab, pembrolizumab 10mg/kg Q3W statistically significantly improves both PFS and OS

- None of the subgroup analyses carried out on data collected during the KEYNOTE-006 trial reveal any statistically significant differences in outcomes between treatments

- Adverse event rates in the KEYNOTE-006 trial are high for all patients. There are no statistically significant differences in AEs between patients in the pembrolizumab arms compared to those in the ipilimumab arm of the trial

- HRQoL data were collected as part of the KEYNOTE-006 trial; the analyses are not reported in the clinical section of the CS.

Indirect evidence: pembrolizumab vs ipilimumab, vemurafenib and dabrafenib

- The company reports the results of four NMAs which were carried out to compare treatment with pembrolizumab with ipilimumab, vemurafenib and dabrafenib treatment using a method based on fractional polynomials. Dacarbazine was included in the NMAs but was not considered as a relevant comparator

- In the first-line setting, the results of the NMAs show that treatment with pembrolizumab 10mg/kg Q3W may statistically significantly improve PFS (at 3, 6 and 12 months) and OS (at 6 and 12 months, but not at 18 months) compared to treatment with ipilimumab

- In the second-line setting, there is no statistically significant difference in PFS or OS when comparing treatment with pembrolizumab 10mg/kg Q3W with ipilimumab treatment

- For patients with BRAF positive mutations, when comparing treatment with pembrolizumab 10mg/kg Q3W with vemurafenib treatment, the credibility of the results is questionable as the RPSFT method may not have adequately adjusted for patient crossover

- In terms of PFS or OS for patients with BRAF mutation positive tumours, there are no statistically significant differences in outcomes for either first- or second-line treatments when pembrolizumab 10mg/kg Q3W is compared with dabrafenib.

- As expected, due to a lack of efficacy, pembrolizumab 10mg/kg Q3W treatment is statistically significantly better than dacarbazine in terms of PFS and OS in both the first- and second-line setting.

Key issues and uncertainties

- There is no phase III RCT evidence to support the use of pembrolizumab 2mg/kg Q3W to treat advanced melanoma in patients previously untreated with ipilimumab in either a first- or second- line setting. The ERG cautiously accepts the EMA's statement that the 2mg/kg Q3W and 10mg/kg Q3W doses of pembrolizumab are clinically equivalent when used to treat advanced melanoma in this patient population

- The KEYNOTE-006 trial was stopped early due to the demonstrated net survival gain of pembrolizumab10mg/kg Q3W over ipilimumab. This means that the available OS data are immature and the true impact on OS may never be fully known. The ERG notes that there is evidence[41,58] that trials which were stopped early for benefit have been shown **not** to reach the expected survival gain estimated at the time of stopping.

- In the KEYNOTE-006 trial, the original RCT protocol stated that patients would only be treated with pembrolizumab 10mg/kg Q3W for 24 months. As the trial was stopped early, the investigators could not enforce this stopping rule. The ERG is unsure of the consequences of this course of action

- The company performed four NMAs using fractional polynomials. The ERG is not confident that the results of the NMAs are valid due to observed methodological weaknesses in the way this approach was used.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by Merck Sharp & Dohme in support of the use of pembrolizumab for treating unresectable, metastatic melanoma in people previously untreated with ipilimumab. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company also provided an electronic copy of their economic model that was developed in Microsoft Excel.

5.2 The company's review of cost effectiveness evidence

5.2.1 Objective of cost effectiveness review

The company undertook searches to identify studies reporting the cost effectiveness of comparator therapies to pembrolizumab for the treatment of patients with advanced melanoma. Details of the search strategies employed by the company are included in Appendix 15 of the CS. The databases and the initial time horizon for each search are summarised in Table 33. In all cases the searches were updated in March 2015.

Table 33 Database search details

Database searched	Initial time horizon*
Medline (via OVID SP)	1946 to July 2014
Medline In-process (via OVID SP)	
EMBASE	1974 to July 2014
The Cochrane Library (including the NHS EED and HTA databases)	Searches to July 2014
Econ-Lit	1886 to July 2014

*An updated search of all databases was undertaken in March 2015
EED=economic evaluation database; HTA=health technology assessment

Hand searches were also performed from the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conferences. These were constrained to the most recent 2 years (from July 2014) and updated searches were carried out in March 2015. In addition, the NICE website[59] was searched to identify relevant information from previous submissions.

5.2.2 Eligibility criteria used in the study selection

The inclusion/exclusion criteria used to select studies are presented in Table 34. The ERG is satisfied that these criteria are relevant to the decision problem.

Table 34 Economic evaluation search inclusion/exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	Patients with advanced melanoma who are naïve to treatment with ipilimumab	None
Interventions	Any medical treatment of advanced melanoma, or best supportive care, no treatment or placebo	Non-pharmacological interventions
Outcomes	Studies including a comparison of costs between the intervention and comparator arms. Results should also include either incremental QALYs (or another measure of health outcome/clinical effectiveness), or be structured with a cost minimisation argument	Cost-only outcomes (without a cost-minimisation argument, e.g. burden of illness studies)
Study type	Full economic evaluations, comparing at least two interventions in terms of cost consequence, cost minimisation, cost effectiveness, cost utility or cost benefit	Reviews (systematic or otherwise), letters and comment articles
Publication type	Economic evaluations	Burden of illness studies
Language restrictions	Studies for which a full text version is available in English	Not available in English
Other	Studies must present sufficient detail of the methodology used and provide extractable results	Studies that fail to present sufficient methodological detail, such that the methods cannot be replicated or validated. Studies that fail to present extractable results

QALYs=quality adjusted life years
Source: CS, Table 65

5.2.3 Included and excluded studies

The company did not identify any relevant studies for inclusion in the review.

5.2.4 Conclusions of the cost effectiveness review

The company suggests that the lack of relevant studies can be explained by the fact that a positive NICE recommendation for the use of ipilimumab for previously untreated unresectable melanoma (TA319[13]) was only published in July 2014 (less than a year before the CS was sent to NICE).

5.2.5 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and stated inclusion/exclusion criteria and is confident that the company did not miss any relevant published papers.

The ERG acknowledges that, within the cost effectiveness section of their report, the company provides details of the methods and results for searches carried out to identify HRQoL associated with advanced melanoma as well as resource requirements and costs

associated with the treatment of advanced melanoma. The ERG considers these details to be very helpful.

5.3 Overview of company's economic modelling

5.3.1 NICE reference case checklist

Table 35 NICE Reference case checklist completed by ERG

Attribute	Reference case[60]	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope[32] developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Patient related direct health effects are considered. No impact on carers has been considered in the model
Perspective on costs	NHS and PSS	Partial. The model only includes NHS costs. Personal Social Service costs have not been considered
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Cost effectiveness analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 30 year time horizon
Synthesis of evidence on health effects	Based on systematic review	No – data have primarily been taken from a single clinical trial
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs and the EQ-5D instrument has been used to collect HRQoL data
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes - HRQoL data were collected as part of the KEYNOTE-006 trial
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes - NHS costs, valued at relevant prices, have been used. PSS costs are not included in the model
Discounting	The same annual rate for both costs and effects (currently 3.5%)	Benefits and costs have been discounted at the 3.5% rate

HRQoL=health-related quality of life; PSS=Personal and Social Services; QALY=quality adjusted life year

5.3.2 Drummond checklist

Table 36 Critical appraisal checklist for the economic analysis completed by ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Partially	The company compares pembrolizumab 2mg/kg Q3W versus comparators; however, the only relevant RCT data available are from the use of pembrolizumab 10mg/kg Q3W
Was a comprehensive description of the competing alternatives given?	Partially	Vemurafenib and dabrafenib were described in the CS; however, the indirect methodology used to compare pembrolizumab with these treatments is not clear from the CS or from the submitted model
Was the effectiveness of the programme or services established?	Yes	The ERG had to cautiously accept the EMA's statement that 2mg/kg Q3W and 10mg/kg Q3W doses of pembrolizumab were clinically equivalent as the clinical trial evidence used to inform the submitted model was based on data derived from KEYNOTE-006 (10mg/kg Q3W)
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Partially	The ERG revised the following parameter estimates in the company's model: OS, PFS, TTD, utility values, drug doses and drug administration costs
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic and probabilistic sensitivity analyses were undertaken
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

CS=company submission; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation

5.3.3 Description of company's economic model

A schematic of the company's submitted economic model is provided in the CS and is reproduced in Figure 3. The company's model compares pembrolizumab with ipilimumab, vemurafenib and dabrafenib. The company's cost effectiveness model is a partitioned survival model which comprises three mutually exclusive health states: pre-progression (i.e. progression-free survival [PFS]), post-progression survival (PPS) and death. All patients enter the model in the pre-progression state. At the beginning of each time period patients can either remain in the same health state or progress to a worse health state, i.e. patients in the pre-progression state can either move to the post-progression state or the death

health state, whilst patients in the post-progression state can only move to the death health state.

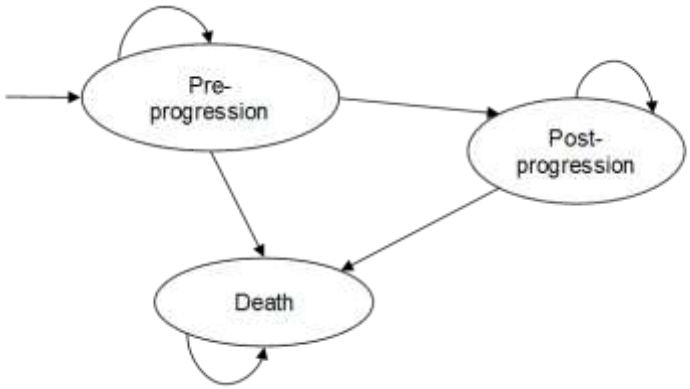


Figure 3 Schematic of company's model
Source: CS, Figure 21

The model uses the partitioned survival (also known as area under the curve or AUC) method to determine the proportion of patients in each of the three health states during each model cycle. The proportion of patients in PPS state is estimated as the difference between OS and PFS.

For patients receiving either pembrolizumab or ipilimumab estimates of PFS and OS were based on survival data from the KEYNOTE-006 trial. The KEYNOTE-006 trial comprises three arms: pembrolizumab 10mg/kg Q2W, pembrolizumab 10mg/kg Q3W and ipilimumab 3mg/kg Q3W. The licensed dose for pembrolizumab is anticipated to be 2mg/kg Q3W and the company assumes in the base case that a dose of 2mg/kg Q3W has the same efficacy and AE profile as a dose of 10mg/kg Q3W. The PFS and OS survival estimates for patients receiving vemurafenib or dabrafenib were based on published figures.

In the model, patients are assumed to receive pembrolizumab 2mg/kg, vemurafenib or dabrafenib until progression or ipilimumab for four cycles. It should be noted that the trial protocol for KEYNOTE-006 included a 24-month stopping rule for pembrolizumab, which is not part of the company's base case but is considered as a scenario in the probabilistic sensitivity analysis. It is assumed that once patients progress they will be prescribed BSC. The pre-progression and post-progression health states were associated with specific treatment, resource utilisation and AE costs. Time-to-death sub-states were used to capture patients' quality of life as a function of length of time until death <1 month, 1-3 months, 3-6 months, 6-9 months, 9-12 months and >12 months to death.

The model has been developed in MS Excel and employs a cycle length of 1 week (no half-cycle correction). The time horizon is 30 years and health effects are measured in quality adjusted life years (QALYs). The perspective is that of the NHS and cost and outcomes are discounted at an annual rate of 3.5%.

Variants of the company's model structure have been used in the modelling of metastatic oncology for numerous STAs, including three recent NICE STAs which considered treatments for advanced melanoma (TA268,[14] TA269[15] and TA321[16]).

5.3.4 Population

Baseline characteristics of the modelled population have been extracted from the KEYNOTE-006 trial (Table 37).

Table 37 Model baseline patient characteristics

Patient characteristic	Mean value	Source
Age	60.3 years	KEYNOTE-006
Proportion of male patients	60%	KEYNOTE-006
Average patient weight	78.63 kg	KEYNOTE-006 (European patients)

5.3.5 Intervention and comparator technology

The intervention was pembrolizumab. The company has used the same ipilimumab cost and benefit data for both $BRAF^{V600}$ populations. For patients with $BRAF^{V600}$ wild-type mutations the comparator was ipilimumab, whilst for patients with $BRAF^{V600}$ positive mutations there were three possible comparators, ipilimumab, vemurafenib or dabrafenib. The company does not refer to a mixed population of $BRAF^{V600}$ patients. Information on drug doses and dosing schedules are shown in Table 38.

Table 38 Drug doses and dosing schedules

Drug	Dose	Administration	Frequency	Number of doses
Pembrolizumab	2mg/kg	I.V. over 30 minutes	Every 3 weeks	Until disease progression, intolerable toxicity, confirmed complete response, withdrawal of consent, or they required another form of antineoplastic therapy as determined by investigator
Ipilimumab	3mg/kg	Intravenous infusion over 90 minutes	Every 3 weeks	Up to four doses
Vemurafenib	960mg	4 x 240mg tablets	Twice daily	Until disease progression or development of unacceptable toxicity
Dabrafenib	150mg	2 x 75mg tablet	Twice daily	Until the patient no longer derives benefit or the development of unacceptable toxicity

Source: CS, Section 5.2.4

5.3.6 Perspective, time horizon and discounting

The company states that the economic evaluation was undertaken from the perspective of the NHS and Personal Social Services. The time horizon was set at 30 years and, in line with the NICE Methods Guide to Technology Appraisal,[60] both costs and outcomes were discounted at 3.5%.

5.3.7 Treatment effectiveness

It is stated within the CS that the company's modelling approach relies on data from the KEYNOTE-006 trial and, as a consequence, the effect of 'tumour flare', which will lead to longer PPS, has not been incorporated. The company states that this means that their approach to modelling is conservative.

The description contained within the CS as to how trial data have been incorporated into the model was considered by the ERG to be unclear. The company provided a response to the ERG's request for further information via the clarification process.

A summary of the company's base case survival modelling approaches is presented in Table 39.

Table 39 Summary of the company's base case survival modelling approaches

Treatment	PFS	OS
Pembrolizumab	KEYNOTE-006 trial data are used directly up until week 13 after which data from a Gompertz model are used	KEYNOTE-006 data used up until 1 year, then data from Schadendorf[61] used up until 7 years. Thereafter registry data (Balch 2001[62]) is used adjusted for background mortality[63]
Ipilimumab	KEYNOTE-006 trial data are used directly up until week 13 after which data from a Gompertz model are used	KEYNOTE-006 data used up until 1 year, then data from Schadendorf[61] used up until 7 years. Thereafter registry data (Balch 2001[62]) is used, adjusted for background mortality[63]
Vemurafenib	K-M data from BRIM-3 trial (McArthur[45]) followed by monthly risk of progression week 39+	Digitised K-M data from BRIM-3 trial[45] until week 60, followed by three different monthly risks of death between weeks 61 and 100, weeks 101 and 152 and weeks 153 and 200 (TA319[13]) followed by Balch (2001)[62] registry data adjusted for background mortality[63]
Dabrafenib	K-M data from BREAK-3 trial (Hauschild[25]) followed by monthly risk of progression week 39+	Digitised K-M data from BREAK-3[25] trial until week 60, followed by three different monthly risks of death between weeks 61 and 100, weeks 101 and 152 and weeks 153 and 200 (TA319[13]) followed by Balch (2001)[62] registry data adjusted for background mortality[63]

HR=hazard ratio; PFS=progression-free survival; OS=overall survival; K-M=Kaplan-Meier

Progression free survival

Pembrolizumab and ipilimumab

KEYNOTE-006 K-M data are used to model survival for the first 13 weeks, thereafter data from fitted Gompertz curves are used.

Vemurafenib and dabrafenib

Unadjusted K-M data from the BRIM-3[22,45] (vemurafenib) and BREAK-3[25] (dabrafenib) trials are used to model PFS for the first 39 weeks, after which a monthly risk of progression of 0.2087 is applied to both arms, as used in the vemurafenib STA submission (TA319[13]).

Overall survival

Pembrolizumab and ipilimumab

KEYNOTE-006 trial data are used for year 1. For the period 12months to 7 years, long-term ipilimumab survival data for treatment-naïve patients are used. For the remainder of the model period (years 7 to 30) Balch 2001[62] registry data are used to represent melanoma survival and background UK mortality data are also applied.[63] The implicit assumption is that all patients surviving 1 year of treatment with pembrolizumab have the same future survival

prospects as that observed for patients treated with ipilimumab. The company indicates that they consider this to be a conservative assumption.

Vemurafenib and dabrafenib

First, K-M data from the BRIM-3[45] (vemurafenib) and BREAK-3[25] (dabrafenib) trials are adjusted using the Korn[64] registry algorithm to account for the difference in baseline characteristics between these trials and KEYNOTE-006. These adjusted K-M data are then used to model OS for 60 weeks. Three monthly risks of death from the vemurafenib STA submission (TA319[13]) are used to model survival in both the vemurafenib and dabrafenib arms from 61 to 100 weeks, 101 to 152 weeks and 153 to 200 weeks. Melanoma-specific mortality data (Balch 2001[62]) combined with background mortality data[63] are then used from 201 weeks onwards.

5.3.8 Health-related quality of life

Health-related quality of life data, using the EQ-5D 3L[65] tool, were collected as part of the KEYNOTE-006 trial, at eight different time points, with only one of those time points being after progression (approximately 30 days after the last dose of study drug or before the initiation of a new antineoplastic treatment, whichever came first). Data from the full analysis set (FAS) population (first interim analysis [data cut-off date: 3rd September 2014]) were analysed. Approximately 20% of cases were missing at baseline and approximately 35% were missing at the time of the analysis. Only completed records were included in the analysis. The UK time trade-off (TTO) value set[66] was used to calculate utility values.

In the base case scenario time to death utilities were the pooled values from the 10mg/kg Q3W pembrolizumab arm and the ipilimumab arm. This choice was justified based on the fact that there was no statistically significant difference in quality of life between these two arms.

HRQoL was age-adjusted using the annual utility decrement of 0.0039 that has been calculated based on figures from Kind.[67] Based on the baseline age of patients included in the KEYNOTE-006 trial, this decrement was applied annually from the age of 60 to 75 years to reflect the natural decrease in utility associated with increasing age.

The utility values used in the company's model are based on time to death rather than disease status (i.e. progression free or progressed). The company made this design choice as an analysis showed that, in terms of mean utility, there was very little difference between

the score associated with PFS and that associated with progressed disease (0.74 and 0.68 respectively).

Patient EQ-5D scores collected during six time periods were used to estimate the mean utility associated with each period. In the base case, the analyses for each of the time periods relating to time to death less than 360 days used data that were associated with a known death date. However, for the category of 360 or more days to death all patients, including censored patients, were included in the analysis.

Table 40 Mean EQ-5D utility scores by time to death

Time to death (days)	Mean (pooled)	95% CI
≥360*	0.82	0.79 to 0.84
[270, 360)	0.71	0.63 to 0.79
[180,270)	0.66	0.60 to 0.72
[90, 180)	0.66	0.60 to 0.71
[30, 90)	0.57	0.49 to 0.65
<30	0.33	0.11 to 0.55

*This group also includes patients who did not die within the trial and report EQ-5D at any time
Source: CS, Table 77 and Appendix 20 (Table 4)

The company carried out a systematic review to identify studies reporting HRQoL for patients with advanced melanoma. As no studies assessing patients who were naïve to treatment with ipilimumab before entering the study were identified, the search was widened to include patients with advanced melanoma. Eleven studies[68-78] were identified. However, only one paper[73] collected data using the EQ-5D tool from a UK population with advanced melanoma. The company considers that, overall, the utilities derived from the KEYNOTE-006[79] trial are comparable to those found in other trial based studies.

5.3.9 Disutility associated with adverse events

It has been assumed by the company that any impact of AEs on HRQoL has been captured within the EQ-5D scores obtained from the KEYNOTE-006 trial and no further decrement has been applied. The company considers that this is a conservative assumption as pembrolizumab has a favourable AE profile in comparison to ipilimumab, vemurafenib and dabrafenib.

5.3.10 Resources and costs

Therapy costs

Pembrolizumab was assumed to be administered at a dose of 2mg/kg every 3 weeks until disease progression, intolerable toxicity, confirmed complete response, withdrawal of consent, or they required another form of antineoplastic therapy as determined by investigator. The list price for pembrolizumab, pending confirmation from the Department of Health, is £1,315 per 50mg vial. However, the company is offering a Patient Access Scheme (PAS) discount of [redacted] which reduces the cost per 50mg vial to £[redacted]. The PAS price of pembrolizumab is used all of the company's cost effectiveness analyses.

Ipilimumab is assumed to be administered to patients at a dose of 3mg/kg every 3 weeks for four cycles. The list price for a 50mg/10ml vial is £3,750.

Weight and sex information for European patients included in the KEYNOTE-006 trial have been used to estimate the number of vials required per patient treated. It has been estimated that for patients receiving pembrolizumab and ipilimumab, the number of vials used per patient treated are 3.7 and 5.7 respectively. In the base case no vial sharing has been assumed. KEYNOTE-006 dose interruption and early stopping data due to toxicity were analysed and results were used to estimate the proportion of patients receiving the expected dose of treatment.

The recommended dose for vemurafenib is 960mg (4 x 240mg tablet) twice daily, i.e. a total daily dose of 1920mg. Vemurafenib is sold as a pack of 56 x 240mg tablets which has a list price of £1,750. Patients are treated with vemurafenib until disease progression or the development of unacceptable toxicity. Within the model patients are assumed to receive 100% of the expected dose.

The recommended dose for dabrafenib is 150mg (2 x 75mg capsule) twice daily, i.e. a total daily dose of 300mg. Dabrafenib is sold in packs of 28 x 50mg capsules or 28 x 75mg capsules which have list prices of £933.33 and £1,440 respectively. Patients are treated with dabrafenib until they no longer derive benefit or the development of unacceptable toxicity. Within the model patients are assumed to receive 100% of the expected dose.

Therapy costs and the proportion of patients receiving the expected dose are summarised in Table 41 and Table 42 respectively.

Table 41 Treatment cost per vial/pack

Treatment	Pack/vial details	Cost per pack/vial	Source
Pembrolizumab	50mg vial	[redacted]	Pending confirmation from Department of Health
Ipilimumab	10ml (50mg) vial	£3,750	MIMS 2015[80]
	40ml (200mg) vial	£15,000	
Vemurafenib	240mg 56-tab pack	£1,750	MIMS 2015[80]
Dabrafenib	50 mg, 28-cap pack	£933.33	MIMS 2015[80]
	75 mg, 28-cap pack	£1,400	

Source: CS, Table 81

Table 42 Proportion of patients receiving expected dose

Treatment	Proportion receiving expected dose	Source
Pembrolizumab	87.7%	KEYNOTE-006
Ipilimumab – dose 1	100.0%	KEYNOTE-006
Ipilimumab – dose 2	96.0%	KEYNOTE-006
Ipilimumab – dose 3	86.6%	KEYNOTE-006
Ipilimumab – dose 4	81.3%	KEYNOTE-006
Vemurafenib	100.0%	Assumption
Dabrafenib	100.0%	Assumption

Source: CS, Table 80

Administration costs

Drug administration costs have been sourced from NHS reference costs[81] and are shown in Table 43. Other costs relating to the administration of drugs are displayed in Table 44.

The company notes that the administration time for pembrolizumab is 30 minutes, whilst that for ipilimumab is 90 minutes. In addition, on each occasion before ipilimumab is administered, patients are required to receive liver and thyroid function tests. The company therefore, considers that pembrolizumab is 'simple' to deliver whilst ipilimumab is 'complex'.

The company model assumes that a month's supply of the oral chemotherapies (vemurafenib or dabrafenib) is initially provided in an outpatient setting (Deliver exclusively oral chemotherapy [SB11Z]). Subsequent doses are assumed to be taken at home with repeat prescriptions' collected from the hospital (no appointments required). It is assumed that it will take a hospital pharmacist 12 minutes to check and dispense each prescription.

Table 43 Drug administration costs

Treatment	Type of administration (NHS Reference Costs 2013/2014[81])	Daycase or outpatient?	Which cycles?	Cost
Pembrolizumab	Simple parenteral chemotherapy at first attendance (SB12Z)	Daycase and regular day/night	All cycles	£245.17
Ipilimumab	Deliver more complex parenteral chemotherapy at first attendance (SB13Z)	Daycase and regular day/night	All cycles	£316.95
Vemurafenib	Deliver exclusively oral chemotherapy (SB11Z)	Outpatient	First cycle only	£136.48
Dabrafenib	Deliver exclusively oral chemotherapy (SB11Z)	Outpatient	First cycle only	£136.48

Source: CS, Table 83

Table 44 Other administration related costs

Type of cost	Available published cost	Model cost per administration	Source
Ipilimumab - liver and thyroid tests performed prior to administration of each dose of chemotherapy	Single complete metabolic panel	£1.00	NHS Reference Costs 2013/14
Vemurafenib and dabrafenib - dispensing cost applied to all but first cycle (12 minutes of pharmacist time)	Hospital pharmacist cost for direct clinical patient time including qualifications (£96/hour)	£19.20	PSSRU 2014

Source: CS, Table 82

Health state unit costs and resource use

The company has estimated resource use costs using data collected as part of the MELODY study.[82] These data have previously been used in the model considered in an appraisal of the use of ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA319[13]). The company notes that although these data are probably out of date they are still the most appropriate as no alternative sources were identified by the search for economic literature. Depending on the health state patients were in, the use of resources related to outpatient and inpatient care, home care, radiologic exams and terminal care. Costs listed in the company's model are summarised in Table 45 and full details are presented in Appendix 26 of the CS.

Table 45 Summary of resource use costs

Category	Cost	One-off or per cycle?
First-line treatment initiation	£1,015	One-off
While receiving treatment (first or second line)	£55	Per cycle
When patients are not receiving treatment	£111	Per cycle
While receiving palliative care	£403	Per cycle
Terminal care - applied on death	£4,580	One-off

Source: Company's model

Adverse event costs

The company model includes grade 3 or 4 AEs experienced by more than 3% of patients and also those that were considered to be expensive to manage. Incidence data were taken from trial data (the KEYNOTE-006 trial for AEs associated with treatment with either pembrolizumab or ipilimumab and the BRIM-3[22,45] and BREAK-3[25] trials for AEs associated with treatment with vemurafenib and dabrafenib respectively). The cost of treating thrombocytopenia was taken from NHS Reference Costs 2013/14[81] and all other costs were values used in the TA319[13] model inflated to 2014 prices (using the Hospital and Community Health Services (HCHS) index[83]).

Table 46 Adverse event costs

Adverse event	Average cost/patient	Source
Fatigue	£200.79	TA319[13] (inflated to 2014 costs)
Diarrhoea	£491.26	TA319[13] (inflated to 2014 costs)
Rash	£137.31	Vemurafenib submission[15]
Nausea and vomiting	£213.49	TA319[13] (inflated to 2014 costs)
Arthralgia	£171.86	NHS Reference Costs 2013/14[81]
Colitis	£1,011.21	TA319[13] (inflated to 2014 costs)
Myalgia/pain	£171.86	NHS Reference Costs 2013/14[81]
Skin reaction	£252.82	TA319[13] (inflated to 2014 costs)
Respiratory distress/pulmonary oedema	£1,767.57	NHS Reference Costs 2013/14[81] (as per TA269[13,15])
Anaemia	£376.61	TA319[13] (inflated to 2014 costs)
Endocrine disorders	£487.17	TA319[13] (inflated to 2014 costs)
Neutropenia	£629.42	TA319[13] (inflated to 2014 costs)
Palmar-plantar erythrodysesthesia	£137.31	Assumed to have the same cost as Grade 3 or higher rash (as TA321[16])
Pyrexia	£3,487.13	NHS Reference Costs 2013/14[81]
Squamous cell carcinoma	£164.36	NHS Reference Costs 2013/14[81] (as TA269[13,15])
Keratocanthoma	£164.36	NHS Reference Costs 2013/14[81] (as per TA269[13,15])
Thrombocytopenia	£316.00	NHS Reference Costs 2013/14[81]
Leukopenia	£0.00	Assumption
Hypotension	£0.00	Assumption
Dyspnoea	£0.00	Assumption
Photosensitivity	£0.00	Assumption
Hyponatremia	£0.00	Assumption
Platelet count decreased	£0.00	Assumption

Source: CS, Table 84

5.3.11 Model validation

Clinical benefit

The company compared outcomes from the KEYNOTE-006 trial with outcomes generated by their model and considered them to be similar.

Expert validation

The company reports that the model approach and inputs are similar to those used in the ongoing CS for pembrolizumab in patients previously treated with ipilimumab [ID760[84]]. The model used in the ongoing pembrolizumab second-line STA submission was validated by an external health economist, a leading expert in health economic practice and methodology

development in the UK as well as member of a NICE ERG. In addition, the accuracy of the implementation and programming of the model was verified via internal quality control processes using an internal quality control checklist.

5.3.12 Results included in company submission

Predicted (per patient) resource use costs included in the company's model are presented in Table 47.

Table 47 Summary of predicted resource use by category of cost

Cost category	Pembrolizumab	Ipilimumab*	Vemurafenib**	Dabrafenib**
Treatment	£46,644	£71,113	£60,929	£45,195
Administration	£3,425	£1,860	£5,636	£5,814
Resource use	£26,576	£24,794	£16,735	£19,910
Adverse events	£44	£106	£83	£110
Total	£76,689	£97,873	£83,384	£71,029

*Independent of BRAF status
**For patients with $BRAF^{V600}$ positive mutations
Source: CS, Tables 93 to 95

The incremental cost effectiveness ratio (ICER) generated by the company's economic model for patients with $BRAF^{V600}$ wild-type mutations is presented in Table 48 and the ICERs for the population of patients with $BRAF^{V600}$ positive mutations are presented in Table 49.

The model results show that, for patients with $BRAF^{V600}$ wild-type mutations, use of pembrolizumab leads to a lifetime decrease in cost to the UK NHS of £21,185 per patient versus ipilimumab. It also offers an additional 0.71 life years and 0.44 QALYs per patient. This means that ipilimumab is dominated by pembrolizumab.

The incremental results show that, for patients with $BRAF^{V600}$ positive mutations, when pembrolizumab is compared to dabrafenib it leads to a lifetime increase in cost to the UK NHS of £5,660 per patient. In addition, it offers an additional 1.67 life years and 0.97 QALYs per patient. The resultant ICER for this comparison is £5,852 per QALY gained. The company's incremental analysis also shows that, for this population, both vemurafenib and ipilimumab are dominated by pembrolizumab.

Table 48 Company's base case results for patients with $BRAF^{V600}$ wild-type mutations (including PAS for pembrolizumab only)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER versus baseline (QALYs)	ICER (£)/(QALY)
Pembrolizumab	£76,689	5.08	3.14	-	-	-	-	-
Ipilimumab	£97,873	4.37	2.69	£21,185	-0.71	-0.44	Dominated	Dominated

Inc=incremental; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, Table 86

Table 49 Company's base case results for patients with $BRAF^{V600}$ positive mutations (including PAS for pembrolizumab only)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER versus baseline (QALYs)	ICER (£)/(QALYs)
Dabrafenib	£71,029	3.41	2.17	-	-	-	-	-
Pembrolizumab	£76,689	5.08	3.14	£5,660	1.67	0.97	£5,852	£5,852
Vemurafenib	£83,384	2.74	1.73	£6,695	-2.34	-1.40	Dominated	Dominated
Ipilimumab	£97,873	4.37	2.69	£21,185	-0.71	-0.44	£51,336	Dominated

Inc=incremental; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, Table 87

5.3.13 Sensitivity analyses

Deterministic sensitivity analyses

The company carried out a wide range of deterministic sensitivity analyses. Resultant ICERs per QALY gained were generated using the 5% and 95% confidence interval values for the variables (except where indicated otherwise). The ICERs per QALY gained for the ten most influential parameters for the comparison of pembrolizumab with ipilimumab, vemurafenib and dabrafenib are shown in Table 50, Table 51 and Table 52 respectively. In each case the two most influential parameters are the shape and the treatment effect of the Gompertz curve used to model PFS for patients receiving pembrolizumab.

Table 50 Results from the ten most influential sensitivity analyses (pembrolizumab vs ipilimumab)

Parameter	Parameter adjustment		Difference in estimate
	Lower	Upper	
PFS Gompertz shape pembrolizumab	£193,384	-£62,200	£255,583
PFS Gompertz treatment effect pembrolizumab	-£33,419	-£60,243	£26,823
OS Weibull distribution - registry data stage IV constant cycle 261+	-£40,716	-£57,948	£17,231
Proportion receiving expected dose: pembrolizumab	-£52,863	-£43,147	£9,716
Kind utility decrement males 75+	-£53,001	-£44,824	£8,177
Kind utility decrement males 55-64	-£43,010	-£50,722	£7,711
Kind utility decrement females 55-64	-£44,140	-£49,499	£5,360
Kind utility decrement females 75+	-£50,819	-£45,632	£5,187
Proportion receiving expected dose: ipilimumab - dose 4	-£45,532	-£49,601	£4,069
Proportion receiving expected dose: ipilimumab - dose 3	-£45,636	-£49,458	£3,822

Source: Company model

Table 51 Results from the ten most influential sensitivity analyses (pembrolizumab vs vemurafenib)

Parameter	Parameter adjustment		Difference in estimate
	Lower	Upper	
PFS Gompertz shape pembrolizumab	£71,538	-£9,366	£80,904
PFS Gompertz treatment effect pembrolizumab	-£256	-£8,746	£8,491
Monthly risk of progression week 39+: vemurafenib	-£10,352	-£2,290	£8,062
OS monthly mortality risk vemurafenib cycle 61-100	-£7,969	-£3,038	£4,931
OS Weibull distribution - registry data stage IV constant cycle 261+	-£3,324	-£6,930	£3,606
Proportion receiving expected dose: pembrolizumab	-£6,410	-£3,335	£3,076
Resource use costs: medical oncologist	-£6,144	-£3,395	£2,749
Cost of one hour pharmacist time	-£3,435	-£6,105	£2,670
Pharmacist time (minutes)	-£3,435	-£6,105	£2,670
Resource use per month: when patients are not receiving treatment: outpatient: medical oncologist % patients treated	-£6,923	-£4,336	£2,586

Source: Company model

Table 52 Results from the ten most influential sensitivity analyses (pembrolizumab vs dabrafenib)

Parameter	Parameter adjustment		Difference in estimate
	Lower	Upper	
PFS Gompertz shape pembrolizumab	£116,588	-£818	£117,406
PFS Gompertz treatment effect pembrolizumab	£12,403	£81	£12,322
Monthly risk of progression week 39+: vemurafenib	£149	£8,388	£8,238
Proportion receiving expected dose: pembrolizumab	£3,471	£7,934	£4,463
Cost of one hour pharmacist time	£7,789	£3,915	£3,874
Pharmacist time (minutes)	£7,789	£3,915	£3,874
Resource use costs: medical oncologist	£4,521	£7,182	£2,661
% males 51-75 kg	£4,543	£7,165	£2,622
Resource use per month: when patients are not receiving treatment: outpatient: medical oncologist % patients treated	£3,768	£6,271	£2,503
% females 76-100 kg	£6,747	£4,539	£2,208

Source: Company model

Scenario analyses

Thirty-three scenario analyses were undertaken to assess the structural and methodological assumptions implemented in the model. The company reports that the only scenarios which resulted in pembrolizumab not being cost effective related to the $BRAF^{V600}$ mutation positive population and involved using log-normal curves (based on KEYNOTE-006 trial data) to project OS. The company, however, considers these scenarios to be unrealistic as long-term survival for patients receiving ipilimumab was projected below that expected based on published data when using log-normal curves.

The company has considered a wide range of different discounts to the prices of ipilimumab, vemurafenib and dabrafenib and reports that results suggest that, at a willingness to pay threshold of £30,000 per QALY (£50,000 per QALY gained) gained pembrolizumab remains the most cost effective treatment in most of the scenarios up to a discount of 45% (60%) to the cost of the comparator drugs.

Probabilistic sensitivity analyses

The company undertook PSA to derive the mean ICER per QALY gained for patients with $BRAF^{V600}$ wild-type mutations and the population with $BRAF^{V600}$positive mutations. The analyses were carried out using 1000 iterations of the cost effectiveness model.

The results from the PSA for patients with $BRAF^{V600}$ wild-type mutations show that, when compared with ipilimumab, pembrolizumab leads to a lifetime decrease in cost to the UK

NHS of £9,954 per patient. It also offers an additional 0.45 QALYs per patient. This means that ipilimumab is dominated by pembrolizumab.

The company notes that there are a small number of iterations in which the cost associated with pembrolizumab is much higher than the range within which costs for the rest of the simulations lie. The company explains that that this is due to the large amount of uncertainty in the PFS extrapolation using the Gompertz curve fit to the KEYNOTE-006 trial data, which means that, as patients are assumed to receive pembrolizumab until progression, long PFS projections result in very high treatment costs. Such outliers are not seen when pembrolizumab treatment is limited to 2 years.

Results from the PSA, with and without, pembrolizumab treatment duration restricted by time, are shown in Table 53.

Table 53 Incremental cost effectiveness results based on PSA for patients with $BRAF^{V600}$ wild-type mutations (including PAS for pembrolizumab only)

	Total costs	Total QALYs	Incremental costs	Incremental QALYS	ICER
Pembrolizumab treatment not limited by time					
Pembrolizumab	£87,685	3.12	£9,954	-0.45	Dominated
Ipilimumab	£97,639	2.67			
Pembrolizumab treatment limited to 2 years					
Pembrolizumab	£71,265	3.12	£26,526	-0.44	Dominated
Ipilimumab	£97,791	2.67			

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality-adjusted life years
Source: CS, Table 96 and Table 98

The cost effectiveness plane and cost effectiveness acceptability curve (CEAC) for patients with $BRAF^{V600}$ wild-type mutations (no time limit on pembrolizumab treatment duration) are shown in Figure 4 and Figure 5 respectively. The CEAC shows that there is an approximately 89.9% chance of pembrolizumab being cost effective compared to ipilimumab at a threshold of £20,000 per QALY gained. At thresholds of £30,000 and £50,000 per QALY gained, there are 90.5% and 91.6% chances respectively of pembrolizumab being cost effective compared to ipilimumab.

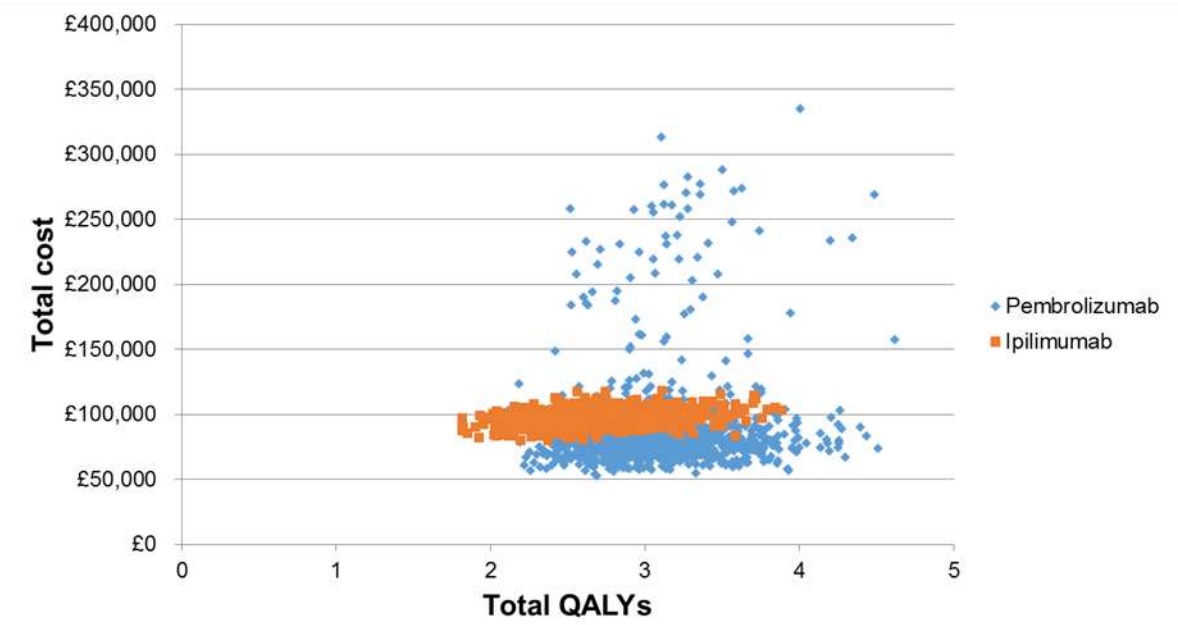


Figure 4 Scatterplot of PSA results for patients with BRAF^{V600} wild-type mutations

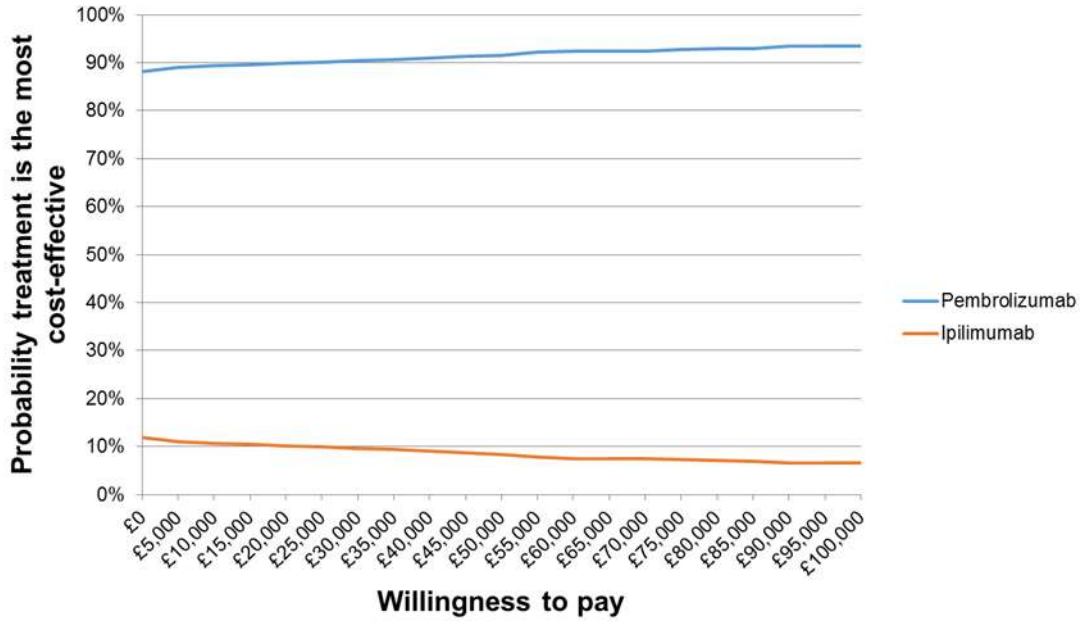


Figure 5 Cost effectiveness acceptability curve for patients with BRAF^{V600} wild-type mutations

The results from the PSA for the population of patients with BRAF^{V600} positive mutations show some variation in terms of the magnitude of both QALYs and costs, compared to the base case, with ipilimumab becoming a dominant option as part of the PSA results (Table 54). For this group of patients (as for patients with BRAF^{V600} wild-type mutations) the PSA results are much higher than the deterministic results and, as for a mixed population of patients with BRAF^{V600} wild- type mutations, the company has determined that this is due to

the high cost of pembrolizumab therapy associated with the iterations in which the PFS projection is optimistic.

Table 54 Incremental cost effectiveness results based on PSA among patients with $BRAF^{V600}$ positive mutations (including PAS for pembrolizumab only)

Technologies	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER	ICER (£)/ (QALY)
Dabrafenib	£71,602	2.19	-	-	-	-
Vemurafenib	£83,939	1.74	£12,338	-0.44	Dominated	Dominated
Pembrolizumab	£87,685	3.12	£16,083	0.93	£17,234	£17,234
Ipilimumab	£97,639	2.67	£9,954	-0.45	£53,525	Dominated

ICER=incremental cost effectiveness ratio; Inc=incremental; QALY=quality adjusted life year
Source: CS, Table 97

The cost effectiveness plane and CEAC for patients with $BRAF^{V600}$ positive mutations are shown in Figure 6 and Figure 7 respectively. The CEAC shows that there is an approximately 80.1% chance of pembrolizumab being cost effective compared to ipilimumab, vemurafenib and dabrafenib at a threshold of £20,000 per QALY gained. At thresholds of £30,000 and £50,000 per QALY gained there are 86.4% and 90.0% chances respectively of pembrolizumab being cost effective compared to ipilimumab, vemurafenib and dabrafenib.

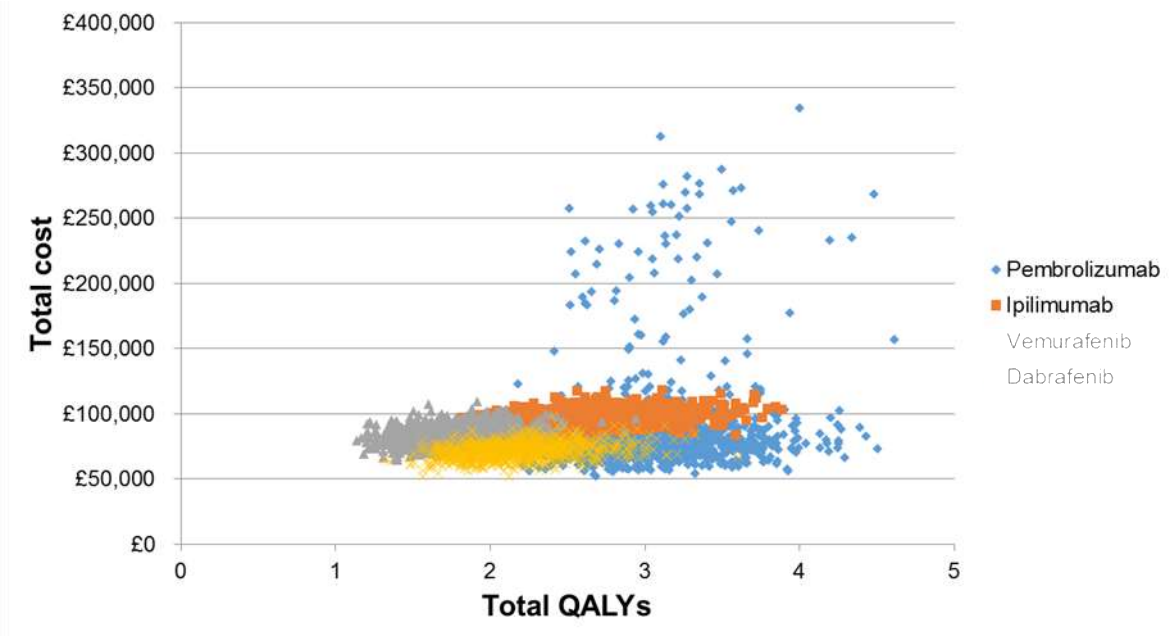


Figure 6 Scatterplot of PSA results for patients with $BRAF^{V600}$ positive mutations

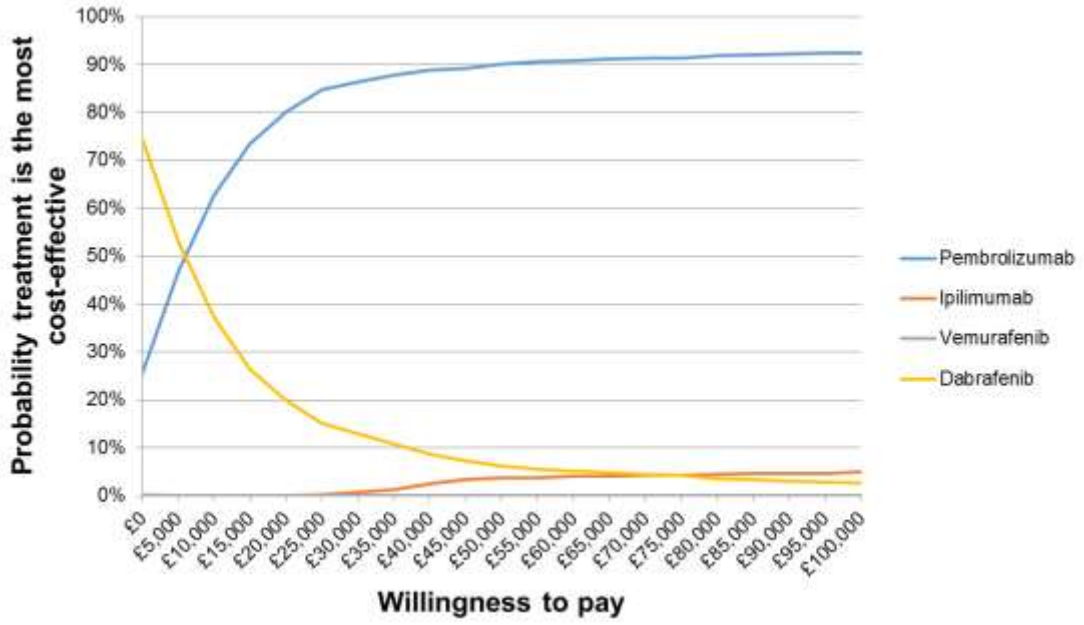


Figure 7 Cost effectiveness acceptability curve for patients with $BRAF^{V600}$ wild- type mutations

5.4 Detailed critique of the company's economic model

5.4.1 Overview

A thorough exploration of the company's economic model has raised a number of concerns. The ERG notes that several of the concerns are the same as those raised by the (same) ERG in a previous ERG report[85] as part of the STA which assessed the use of pembrolizumab for patients previously treated with ipilimumab. As such, some text in this section is a replication or modification of that in the earlier report.[85]

To explore the strengths and weaknesses of the economic model submitted by the company, the ERG has considered which aspects of the model contribute most to the estimate of cost effectiveness (as measured by the ICER per QALY gained) for the comparison of pembrolizumab therapy with ipilimumab (an immunotherapy), vemurafenib (a BRAF inhibitor) and dabrafenib (a BRAF inhibitor).

First, an analysis of the base case results reported in the CS shows that 90.2% of the overall incremental cost saving of pembrolizumab compared to ipilimumab is attributable to differences in direct treatment costs (drug acquisition and administration). Similarly for vemurafenib and dabrafenib the direct treatment costs account for 83.0% and 74.3% of all patient costs (ignoring terminal care costs which are almost identical regardless of the treatment).

This means that only variations in the assumed NHS price or length of treatment of pembrolizumab or comparators can have any meaningful effect on the estimated incremental cost per patient between treatments. The effective NHS price of a new product is determined by the company either by its list price or through a PAS agreed with the Department of Health. The remit of the ERG only extends to checking that the dosing costs have been accurately calculated.

In this appraisal all other cost elements included in the model have no real effect on the size of the ICER per QALY gained. Therefore, the key aspect of the model is the patient benefit claimed by the company as a result of treating patients with pembrolizumab, rather than ipilimumab or either of the BRAF inhibitors, expressed in terms of additional survival time (OS) and QALYs. Given that trial data are only available for 12 months of patient follow up, the methods used to project OS to 30 years have a potentially significant impact on cost effectiveness results. For example, an analysis of the company's base case results shows that 87.5% of the estimated health gain (in terms of additional survival) attributed to treatment with pembrolizumab occurs after 12 months. Thus, the most important element of the company's model is the long-term projection of interim KEYNOTE-006 clinical trial survival results to obtain an expected remaining lifetime for the population.

In addition, it is important to note that the assessment of the cost effectiveness of pembrolizumab versus ipilimumab depends on data from a single phase III clinical trial (KEYNOTE-006) with only 12 months of follow up, which was stopped early for benefit and did not include the anticipated licensed dose of pembrolizumab. These limited data, supported by some data from published sources, have been used as the basis for projecting survival for an additional 29 years.

5.5 Model parameters: overall survival

5.5.1 Critique of overall survival projections

The company uses two general approaches to extrapolate OS: one for pembrolizumab and ipilimumab, and one for vemurafenib and dabrafenib.

Pembrolizumab versus ipilimumab (a mixed population of patients with BRAF^{V600} wild-type and positive mutations): evidence sources

The company's model estimates OS for pembrolizumab and ipilimumab in three distinct phases (Figure 8), each of which uses data from a different source:

- Trial period (0-12 months): KEYNOTE-006 interim analysis
- Mid-term projection (12 months to 7 years): Schadendorf[86] ipilimumab-treatment naïve population data
- Long-term projection (7-30 years): Balch (2001[62]) registry data.

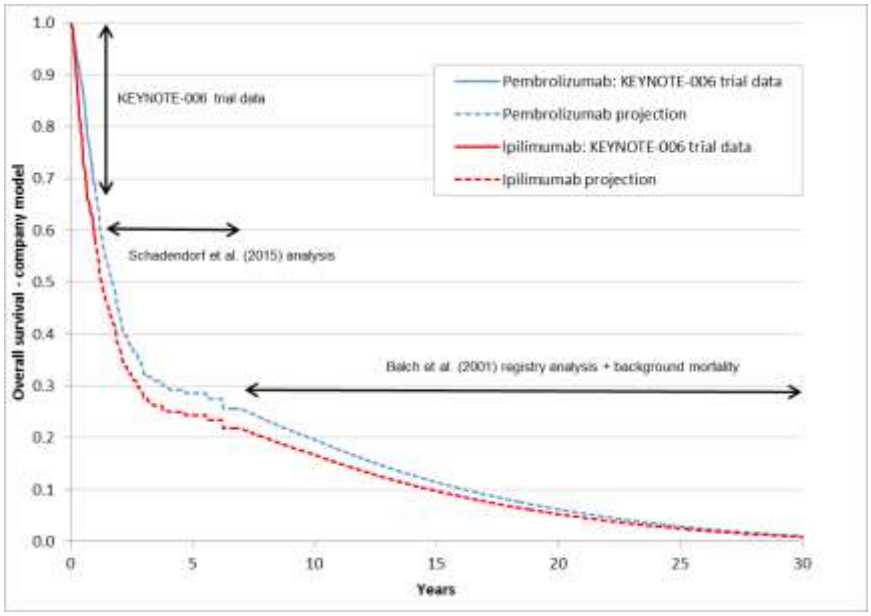


Figure 8: Composition of overall survival data in company's model base case

Trial period (0-12 months): KEYNOTE-006 interim analysis 2

The company has used OS K-M data from the KEYNOTE-006 trial at weekly time points to populate the pembrolizumab and ipilimumab arms of their model. This approach generates an estimated mean survival within the first year for patients treated with pembrolizumab and ipilimumab of 8.21 months and 6.98 months respectively. The ERG has no concerns about the way in which K-M data are used in the model during this time period.

Mid-term projection (12 months to 7 years): Schadendorf

The mid-term projection phase of the company's model uses data reported in a paper by Schadendorf.[86] This paper[86] includes results from a pooled analysis of selected arms from ten phase II and phase III clinical trials, together with two retrospective observational studies, all of which relate to a variety of treatment protocols which include the use of ipilimumab. The population in three of the clinical trials and in both observational studies included ipilimumab-treatment naïve patients.

In the company's model, data relating to pooled survival of ipilimumab-treatment naïve patients from 12 months to 7 years were derived by digitising the relevant OS curve displayed in the Schadendorf[86] paper. The mortality trend was estimated and used by the company to represent OS for both the pembrolizumab and ipilimumab arms of the model for

the same time period (12 months to 7 years). The use made by the company of the results reported by Schadendorf[86] assumes that the multiple sources of heterogeneity evident in the pooled studies (different ipilimumab dosing, various co-medications, use of retreatment and/or maintenance therapy, trial or retrospective observation) have no influence on long-term survival. Examination of the cited references in the Schadendorf[86] paper reveals that, for the subgroup of patients used to populate the company's model, the reported follow-up is generally 3 years or less, and the maximum time period, which is reached in only one study, is 4 years and 7 months. It therefore appears that additional follow-up information must have been obtained from some of these studies. The ERG considers that there is a large risk of uncontrolled selection bias in the conduct of the Schadendorf[86] study.

Long-term projection (7 to 30 years): Balch (2001) registry data

In the company's model the same melanoma-specific mortality rates are applied to surviving patients in both the pembrolizumab and ipilimumab arms. These rates are derived from a paper (Balch [2001[62]]) describing an analysis undertaken on a large US database of melanoma patients which formed the basis for melanoma staging in the sixth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[87] This exercise was subsequently updated and new findings were published by Balch[5] in 2009 as the basis for an improved classification of melanoma staging in the seventh edition of the AJCC Cancer Staging Manual.[88] The new analysis is based on more than twice as many patients (38,898 compared with 17,600 previously), and includes data for 7972 patients with stage IV disease compared to only 1158 in the previous exercise. This larger group of patients with more advanced disease makes it possible to estimate 10-year survival curves for each of the stage IV subgroups (M1a, M1b, M1c).

The ERG considers there to be two issues with the way the Balch (2001[62]) analyses are used within the company's model. First, by using the data from Balch (2001[62]) rather than Balch (2009[5]), the company's model is unable to incorporate the significant influence of the subgroup casemix on the average life expectancy of a cohort of patients diagnosed with metastatic melanoma, as this information was only captured by the later analysis.

Second, the model applies the registry data as if patients recruited to the KEYNOTE-006 trial are newly diagnosed at the beginning of the trial and so assumes that the survival curve from Balch (2001[62]) can be applied from year 7. This, however, is not the case; 34% of patients included in the KEYNOTE-006 trial had been pre-treated with one line of therapy. It is well understood that a large proportion of patients newly diagnosed with metastatic melanoma die within a few months, so, given that this 34% of patients had survived to be

treated with a second line of therapy, they are likely to belong to a subset of 'good survivors' who might be expected to have greater OS than the general population of newly diagnosed patients.

Pembrolizumab versus ipilimumab: projection implausibility

Examination of the projected OS profile and the corresponding changes in the long-term mortality trend (Figure 9) highlights that during the mid-term phase (and the first 3 years of the long-term phase) the mortality trend is erratic and occasionally zero. A zero mortality rate would be remarkable in a fully healthy cohort, but it is implausible to project periods where no-one dies of any cause in a cohort of patients whose metastatic disease has progressed after at least one phase of treatment. In addition, hazard functions for a real-world cohort of patients change slowly over time unless there is a clear clinical reason for all patients to experience a sudden alteration at the same time - usually due to the trial protocol. The ERG therefore considers that the three-phase method used by the company to project survival for pembrolizumab and ipilimumab is implausible.

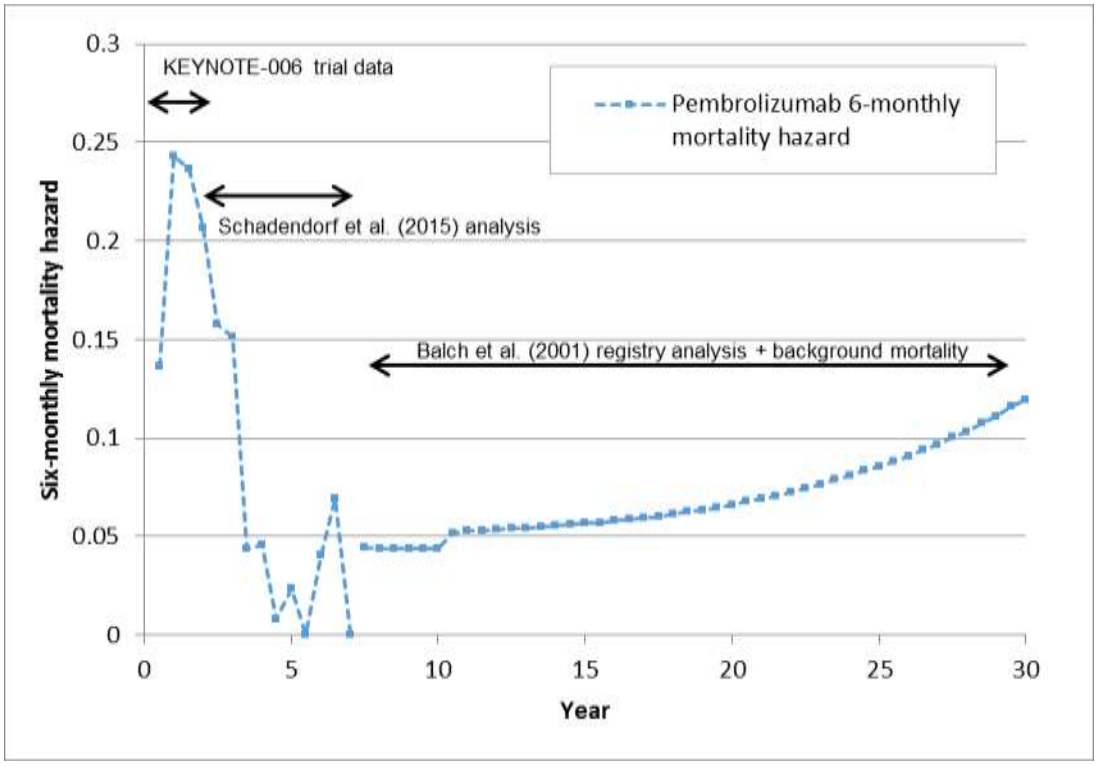


Figure 9: Pembrolizumab 6-monthly mortality in the company's model

Pembrolizumab versus vemurafenib and dabrafenib (patients with $BRAF^{V600}$ positive mutations)

A three-phase approach was also used by the company to project OS for patients with $BRAF^{V600}$ positive mutations treated with vemurafenib or dabrafenib, namely:

1. Period 1 (the first 60 weeks): digitised data from the two main clinical trials that provide evidence for the efficacy of vemurafenib and dabrafenib (BRIM-3[22,45] and BREAK-3 [25]respectively)
2. Period 2: (weeks 61 to 200): monthly risks of death from TA319[13]
3. Period 3 (week 201 onwards): registry data from Balch (2001[62]).

Period 1: the first 60 weeks

A published algorithm (Korn[64]) was used to adjust the digitised data for differences in patient characteristics and/or relative treatment effects between the BRIM-3,[22,45] BREAK-3[25] and KEYNOTE-006 trials. The algorithm used to make the adjustments is based on a meta-analysis of 42 phase II trials. Whilst the ERG considers that this algorithm can be appropriately applied to OS data for patients with advanced melanoma, it suffers from a series of limitations when applied to the patient population specified in the CS, namely:

- The meta-analysis on which the algorithm was estimated relates to studies published pre-2008 and the relevance of its adjustments to patients treated with $BRAF^{V600}$ inhibitors (which were licensed sometime after 2008) is unclear
- The algorithm is for all patients and is not dependent on $BRAF^{V600}$ status
- The meta-analysis only used data from patients with stage IV disease, whilst the population considered in this appraisal is those with stage III or stage IV disease.

In view of these concerns, the ERG does not consider that the survival estimates for either vemurafenib or dabrafenib which have been generated using the Korn[64] algorithm have been appropriately adjusted to allow a valid comparison with pembrolizumab and must, therefore, be considered unreliable. This view is supported by findings from research[89] which suggest that results from unadjusted indirect treatment comparisons (ITCs), even if the ITC includes RCTs, should be viewed as being as robust as results generated from observational studies.

Period 2: week 61 to week 200

In light of the paucity of data, the ERG is satisfied that the approach used by the company, i.e. using monthly risks of death from TA319,[13] was appropriate.

Period 3: week 201 onwards

The changes that can be made to address the lack of comparable OS data for vemurafenib and dabrafenib within the submitted model are limited. However, the ERG considers that, for consistency with pembrolizumab and ipilimumab, data from Balch (2009[5]) rather than Balch (2001[62]) should be used for the whole extrapolation phase beyond the period for which trial data (obtained by digitising graphs available in published papers) are available. It should be

noted that such an approach does not address the methodological weaknesses of the algorithm published by Korn[64] when applied to patients with $BRAF^{V600}$ positive mutations with stage III or IV disease.

5.5.2 Life table mortality rates (a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations)

The company's model uses published annual life table estimates for England and Wales[63] to represent non-melanoma related causes of death in long-term survival projections (7 to 30 years). Separate mortality rates for males and females are weighted for the gender balance of patients participating in the KEYNOTE-006 trial for each year of age from 50 to 100 years. This approach is flawed because mortality is systematically lower for females than for males so that, over time, the gender balance shifts in favour of females. The ERG considers that not making allowance for this drift leads to an over-estimate of mortality for the cohort as a whole.

5.6 Model parameters: progression-free survival

5.6.1 Critique of progression-free survival evidence sources used in projections

Pembrolizumab versus ipilimumab (a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations)

The model uses PFS data from independent central IRO assessment. However, the ERG considers that it would have been more appropriate to use INV assessment as local assessment is more representative of clinical practice than independent central IRO assessment. In addition, the ERG suggests that it would have been more appropriate to use an alternative non-informative right-censoring rule to avoid biasing PFS estimates.

In the pembrolizumab and ipilimumab arms of the company's model, K-M trial data are used directly until week 13 (91 days), and thereafter a Gompertz model is applied to project PFS indefinitely. The Gompertz model is based on the assumption of Cox proportional hazards. However, as described in Section 5.7.3 and shown in Figure 10, the PFS trial data deviate significantly from the trend that would be expected if the proportional hazards assumption was valid. The ERG therefore concludes that using a simple hazard ratio in the company model as the basis for estimating PFS for patients treated with ipilimumab, and therefore the difference in PFS attributable to pembrolizumab, is invalid. On this basis, the ERG considers the company's base case PFS results based on the proportional hazards assumption are unreliable and an alternative approach that does not rely on proportional hazards should be used.

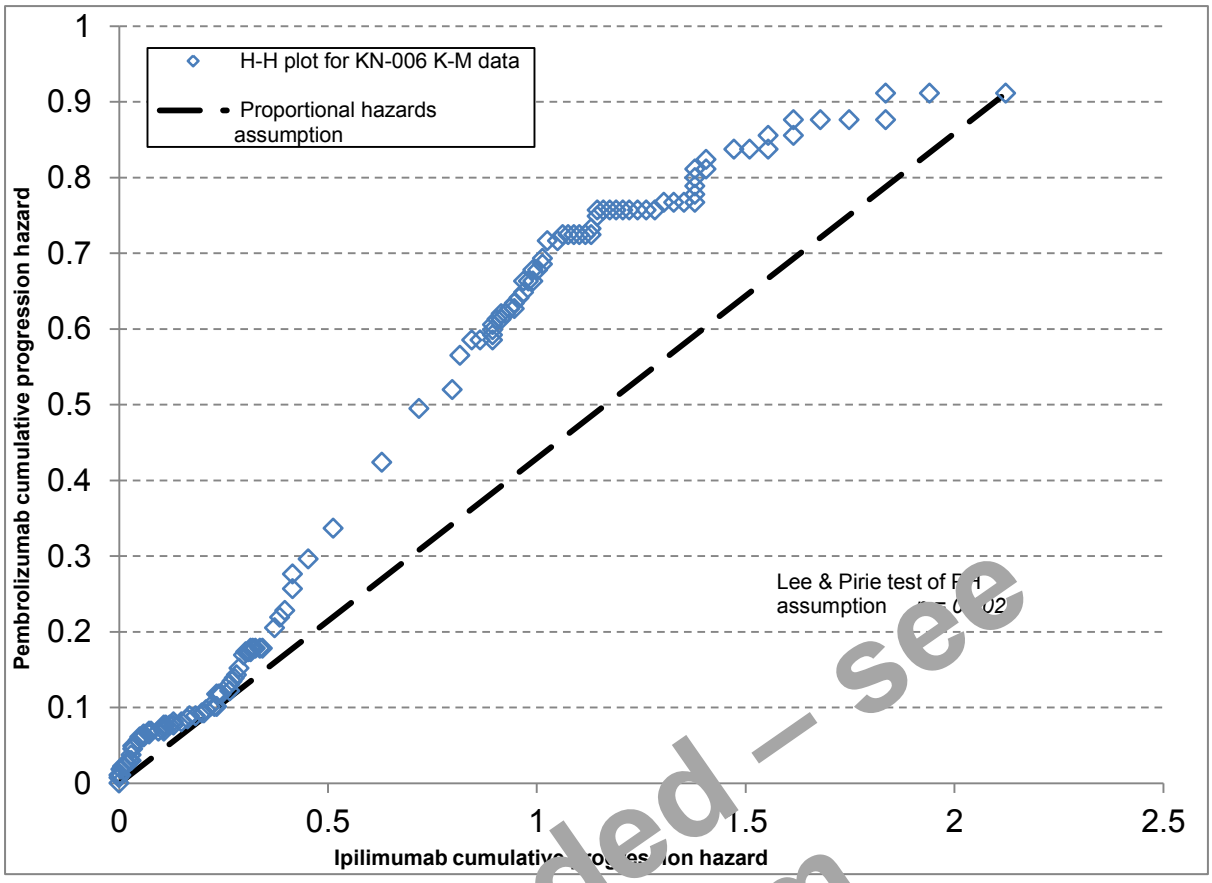


Figure 10 Cumulative mortality hazard plot of KEYNOTE-006 trial arms showing that the assumption that the PFS hazards are proportional is invalid

Pembrolizumab versus vemurafenib and dabrafenib (patients with BRAF^{V600} positive mutations)

For the comparison of pembrolizumab versus vemurafenib and dabrafenib, PFS was estimated using data obtained by digitising published PFS K-M plots from the BRIM-3[22,45] and BREAK-3[25] trials up to 39 weeks, and then using the monthly risk of progression from a recent NICE appraisal which assessed treatment with ipilimumab (TA319[13]). No adjustments have been made for differences in patient characteristics and/or relative treatment effects between the BRIM-3,[22,45] BREAK-3[25] and KEYNOTE-006 trials. The ERG therefore considers that the OS projections for vemurafenib and dabrafenib must be considered unreliable.

5.7 Model parameters: treatment duration (a mixed population of patients with BRAF^{V600} wild-type and positive mutations)

The company's model uses PFS from the KEYNOTE-006 trial as the basis for costing pembrolizumab and ipilimumab treatment; treatment for patients receiving ipilimumab is limited to 12 weeks. In the ERG's experience, using PFS as a proxy for time to treatment

discontinuation (TTD) generally results in an over-estimate of drug usage as patients frequently withdraw from treatment as a result of emergent AEs before any disease progression is identified. The company's model applies single average proportional adjustments to model this effect. However, the ERG considers that using TTD values provides a more accurate estimate of the true cost of treatment.

The ERG has demonstrated in a previous ERG report (TA268[14]) on advanced melanoma that there is a subgroup of patients with metastatic melanoma who live for substantially longer periods than the majority of patients with the disease. The ERG, therefore, has concerns that a simple extrapolation of TTD and PFS data could underestimate the time during which patients receive pembrolizumab treatment as it is plausible that the subgroup who survive for longer could also remain in PFS for longer than most patients.

TTD data were not available for patients with $BRAF^{V600}$ positive mutations receiving vemurafenib or dabrafenib. Therefore, the company used PFS as a proxy for TTD for these groups of patients. Given the ERG's concerns about PFS projections, the fact that TTD data were not available for incorporation into the model further raises the ERG's concerns about the robustness of the cost effectiveness results generated by the company's model for the comparisons of pembrolizumab with vemurafenib and dabrafenib.

5.8 Model parameters: utility values (a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations)

End of life utility values

The utility values used in the company's base case analysis are drawn from EQ-5D responses collected during the KEYNOTE-006 trial and scored according to the UK value set. However, in international trials it is often the case that patient responses to the EQ-5D questionnaire differ significantly depending on the country in which the patients have been treated. The ERG considers the use of UK or European responses only from the KEYNOTE-006 trial would produce utility value estimates that are more relevant to a UK population than those generated using the full dataset.

Decrease in utility associated with disease progression

The ERG considers that whilst previous NICE submissions (eg TA319[13]) in this disease area may not have applied different utilities for the PFS and progressive disease states, this approach leads to the unrealistic situation whereby treatment with pembrolizumab is more cost effective the less effective it is at stopping disease progression. The ERG therefore

considers that, in the absence of being able to construct a new model to address this flaw, it would be appropriate to include pre- and post-progression utilities in the company model.

5.9 Model parameters: dosage calculations (a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations)

Pembrolizumab is prescribed for infusion at a dose of 2mg/kg of body weight Q3W. The distribution of body weight among patients in the KEYNOTE-006 trial (who received a dose of 10mg/kg Q3W) is used to estimate the total number of required doses by dividing patients into weight bands corresponding to whole numbers of vials required. This method should give an accurate result provided that the number of patients is sufficiently large that the balance between bands in the KEYNOTE-006 trial approximates closely to that of the general population with advanced melanoma. However, body weight can vary widely between different countries. For this reason, the ERG is of the opinion that dosages should be recalculated based upon more representative values of UK body weight.

5.10 Model parameters: administration costs (a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations)

In the company's model, the cost of administering systemic treatment is classified according to Healthcare Resource Group (HRG) categories. The ERG has taken clinical advice to determine the most appropriate costing category for each treatment. The advice has been that the time taken to deliver pembrolizumab is the same as that taken to deliver ipilimumab and so the HRG categories should be identical for both treatments.

5.11 Summary of ERG review of the company's model

An analysis of the base case results reported in the CS shows that 90.2% of the overall incremental cost saving of pembrolizumab compared to ipilimumab is attributable to differences in direct treatment costs (drug acquisition and administration). Similarly, for vemurafenib and dabrafenib the direct treatment costs account for 83.0% and 74.3% of all patient costs (ignoring terminal care costs which are almost identical regardless of the treatment). As prices have already been agreed with the Department of Health, the credibility of survival projections is extremely important.

The assessment of cost effectiveness of pembrolizumab vs ipilimumab depends on data from a single phase III clinical trial (KEYNOTE-006) with only 12 months of follow up, which was stopped early for benefit and did not include the anticipated licensed dose of pembrolizumab. These limited data, supported by some data from published sources, have been used as the basis for projecting survival for an additional 29 years.

The ERG considers the OS projections for the comparison of pembrolizumab versus ipilimumab (for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations) to be implausible. Furthermore, the ERG considers that the PFS and OS estimates for the comparison of pembrolizumab with vemurafenib and dabrafenib (patients with $BRAF^{V600}$ positive mutations) should be considered unreliable.

Other issues identified by the ERG

- PFS data were used to model treatment duration, rather than TTD data which is a more accurate reflection of clinical practice
- Time to death utility values were based on the whole KEYNOTE-006 trial population rather than only the European population
- Patients experienced no decrement, in terms of HRQoL when they entered the progressive disease state
- Doses should have been calculated using a UK population weight distribution rather than trial weight distribution
- The cost of administering pembrolizumab was less than that for administering ipilimumab; they should have been the same.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Overview

The ERG has made the following changes to the company's submitted model to address the points raised in Section 5:

- ERG's preferred OS extrapolation and non-cancer mortality amendment
- ERG's preferred (INV based) PFS estimates
- Treatment duration based on TTD rather than PFS
- Combined progressive disease and time to death utilities (European values)
- Drug dosages based on a UK population
- ERG's preferred drug administration costs.

In addition, the ERG explored two scenarios where TTD and PFS for pembrolizumab were extended further than that projected by a simple extrapolation. These scenarios were included to investigate the effect on cost effectiveness of a hypothesised subgroup of patients who remain in PFS for a longer period than the rest of the patient population.

Details of all revisions made by the ERG to the company's model in Microsoft Excel are presented in Appendix 3.

6.2 ERG's alternative approach to modelling overall survival

The ERG's preferred (mixed exponential) OS extrapolation

The most implausible aspect of the company's three-phase approach is the use of the Schadendorf[86] analysis to extend the modest survival gain seen in the first year of the KEYNOTE-006 trial for a further 6 years. In 2011/12 the Liverpool Reviews and Implementation Group acted as the ERG in the first appraisal of ipilimumab for patients with malignant melanoma (TA268[14]). During this appraisal the company submitted additional evidence drawn from seven of the studies later included in the Schadendorf[86] analysis. In response to this, the ERG submitted an addendum[90] which concluded:

> "The ERG does not consider the pooling of isolated treatment arms across trials to be appropriate…the broader pooling of data from all patients who received ipilimumab, regardless of dosing regimen or patient baseline characteristics, can only result in uninterpretable results of no relevance to the current decision problem."

The Schadendorf[86] paper is an extension of this company analysis, including more studies (especially more observational data) and thereby adds further incompatibility into the

evidence base. The ERG therefore considers the pooled survival analysis reported in this paper[86] to be inherently compromised and unreliable.

In the addendum[90] to the ERG report submitted as part of TA268, the ERG pursued the question of long-term melanoma survival in the light of observations from clinical advisors, and considered whether there may be two distinct sub-populations with contrasting prognoses – a large majority subject to high mortality rates and a small minority with excellent survival prospects extending for several years. The survival curves by Balch et al 2009[5] published in support of the seventh AJCC Melanoma Staging and Classification Manual[88] were used to develop and test an alternative 2-group projection model, based on a mixed exponential function. This proved very effective, accurately replicating the published AJCC results (Figure 11) and the MDX010-020[91] trial. The ERG has subsequently validated this approach using other data sets.

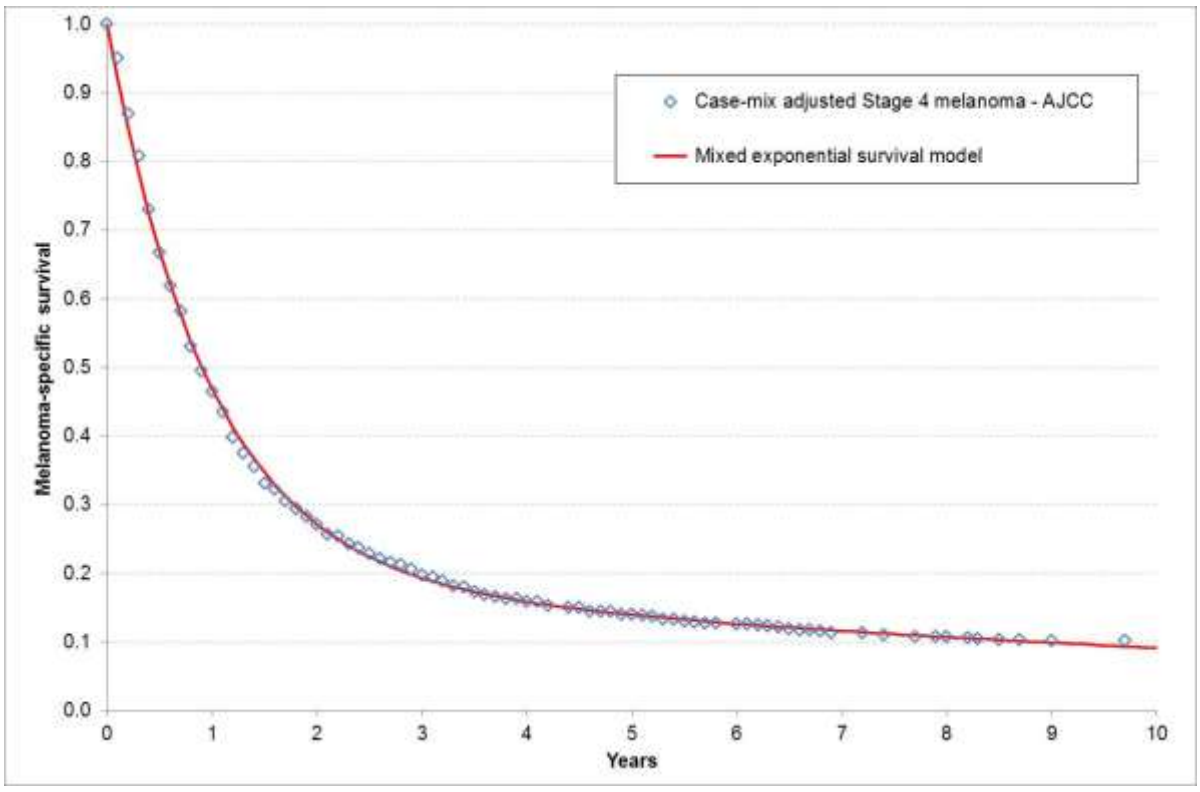


Figure 11 Ten-year survival modelled using a mixed exponential function (ERG's preferred approach)

In the light of these findings, the ERG has applied this method to generate expected survival profiles matched for casemix (M1a: M1b: M1c) for each arm of the KEYNOTE-006 trial as well as for vemurafenib (BRIM-3[22,45]) and dabrafenib (BREAK-3[25]). The appropriate casemix adjusted curves (mixed exponential survival model) were then used for the projection

phases of pembrolizumab and comparators in the company's model (Figure 12). This avoids the serious problems identified by the ERG in the company's model. In addition, this approach can be justified on the grounds that beyond the observed trial period the great majority of patients receiving pembrolizumab cease treatment rapidly due to disease progression or AEs, and future survival will largely be determined by the conventional treatment options current in the AJCC registry era.

When the ERG's method of survival projection and non-cancer mortality is substituted for that used in the company's base case, the estimated QALY gain for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations receiving pembrolizumab compared to those receiving ipilimumab is reduced by 0.05 QALYs. This means that, compared to the base case, the dominance of pembrolizumab over ipilimumab increases with the ERG amendment to OS.

For patients with $BRAF^{V600}$ positive mutations, amending OS resulted in a reduction in the incremental QALY gain associated with pembrolizumab compared to vemurafenib of 0.52 QALYs to 0.88 QALYs. However, pembrolizumab remained dominant compared to vemurafenib.

Comparing pembrolizumab to dabrafenib, the ERG OS amendment increased the QALY gain but by only 0.01 QALYs. However, there was a small decrease in the incremental cost of pembrolizumab compared to dabrafenib of £102. This meant that, on balance, the ICER for pembrolizumab compared to dabrafenib increased by £16 to £5,868 per QALY gained.

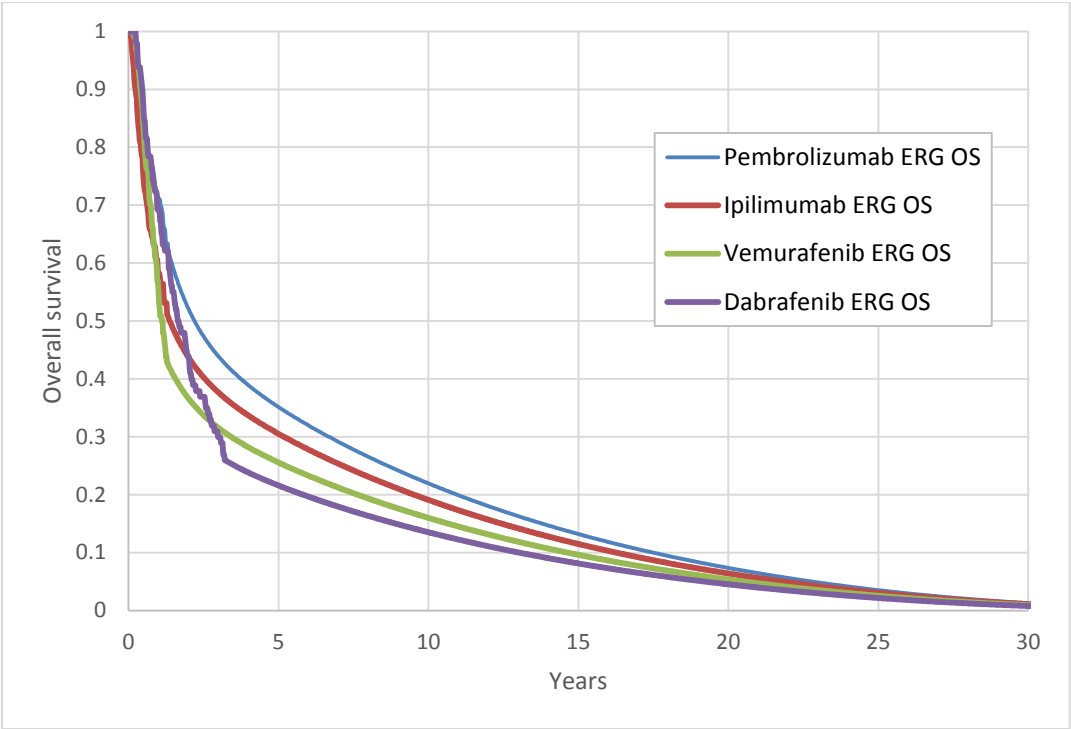


Figure 12 Long-term projection of survival beyond the available trial data, using a mixed exponential model

ERG's exploratory analysis

The ERG undertook an exploratory analysis to estimate the difference in OS between pembrolizumab and ipilimumab (see Appendix 4). It has not been possible to integrate results from the ERG's exploratory analysis into the company model and restructuring the company's model is beyond the ERG's remit. As a result of the analysis, the ERG has concluded that not only were the OS extrapolations undertaken by the company unconvincing, they were also unnecessary if the increase in OS that occurs as a result of treatment with pembrolizumab rather than ipilimumab takes place within the first 8 to12 months of treatment.

Using this method the OS gain from use of pembrolizumab rather than ipilimumab is estimated as 126 days (4.1 months), less than half that estimated in the company's base case scenario (8.6 months). Unfortunately, this approach to estimating OS does not lend itself easily to incorporation into the existing company model without radical redesign, which is beyond the remit of the ERG. Notwithstanding, the ERG is confident that despite this reduction in OS benefit, pembrolizumab remains cost effective compared to all comparators after all of the suggested ERG amendments are made. The principle is, however, clear. A much simpler robust decision model could be constructed on the basis of the available

evidence, avoiding much of the speculative survival modelling currently incorporated in the company's model.

6.2.1 Life table mortality rate adjustment

Non-cancer related mortality is systematically lower for females than for males so that, over time, the gender balance of a cohort will shift in favour of females. If an allowance is not made for this drift then, over time, the mortality for the cohort as a whole will be over-estimated. The ERG has calculated representative mortality rates using dynamic weighting which, when applied in the model, increases the incremental survival and QALYs by less than 1% (0.0002 QALYs for pembrolizumab and comparators). This had no impact on the ICERs per QALY gained for pembrolizumab versus any of the comparators.

Rather than presenting the impact of this change separately in the results tables (Table 55, Table 56 and Table 57), this adjustment has been included in the ERG's preferred approach to modelling OS.

6.3 ERG's preferred progression-free survival estimates

To model PFS for patients receiving pembrolizumab or ipilimumab, the ERG fitted exponential projective models to patient level data (INV PFS) from the KEYNOTE-006 trial, these data were requested from the company. These data were generated using an alternative, non-informative, right-censoring rule to avoid biasing PFS estimates and are shown in Figure 13. No changes were made to the PFS estimates for the two BRAF inhibitors (vemurafenib and dabrafenib) as the ERG could not identify a more appropriate method. It is reiterated that the ERG considers that the methods used in the company's unadjusted analysis to be flawed and undermine the credibility of the results that have been generated by this method.

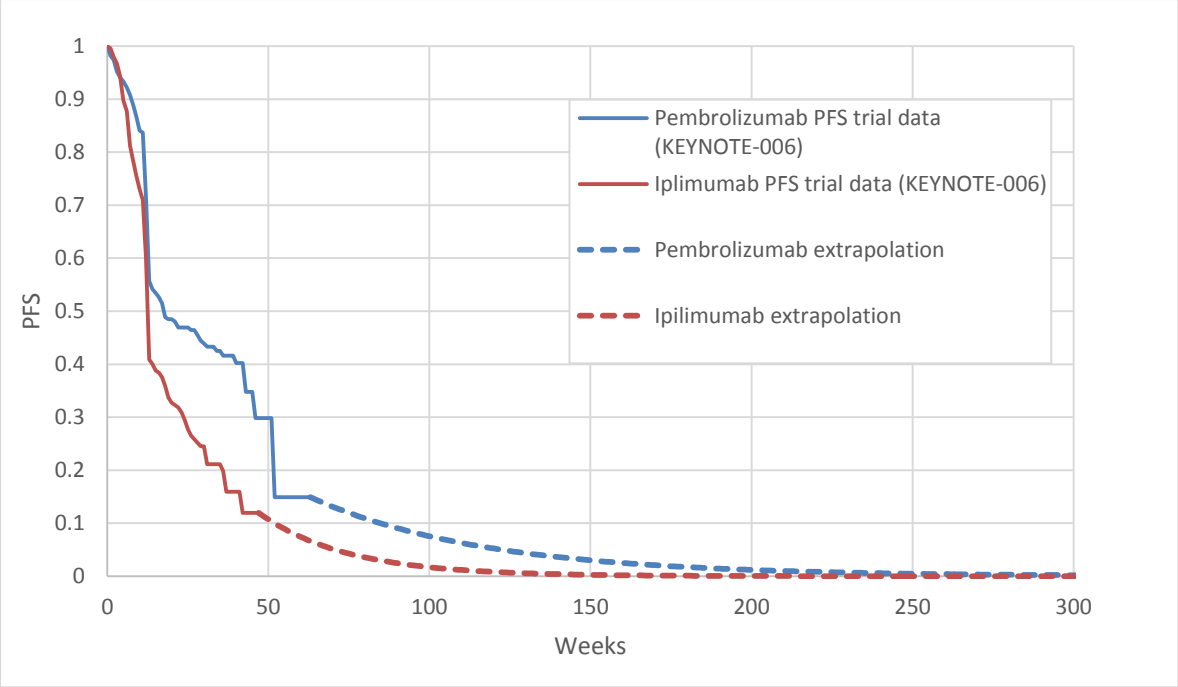


Figure 13 Progression-free survival data (INV) using revised censoring and exponential projection functions

In the absence of any other changes, adjusting PFS resulted only in a change in the costs of pembrolizumab and ipilimumab. The change in the cost of ipilimumab was minimal (only £10 per patient). For pembrolizumab, the change was more substantial increasing costs by £2,442 per patient. This did not, however, change the dominant position of pembrolizumab over ipilimumab for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations, or for pembrolizumab over vemurafenib for patients with $BRAF^{V600}$ positive mutations. For patients with $BRAF^{V600}$ positive mutations, when pembrolizumab is compared to dabrafenib the change increased the ICER to £8,377 per QALY gained.

6.4 Treatment duration

As part of the clarification process, the ERG asked the company to provide results from a K-M analysis of TTD for both the Q2W and Q3W pembrolizumab arms and the ipilimumab arm of the KEYNOTE-006 trial. The ERG explored the effect of pooling the TTD data from both Q2W and Q3W pembrolizumab arms. However, the ERG noticed differences between the two arms. For example, at 12 weeks, 66.8% of patients in the Q3W arm were still receiving pembrolizumab compared with 77.3% in the Q2W arm. By 44 weeks, the proportions still receiving treatment had fallen to just over 29% in both pembrolizumab arms. The difference observed at 12 weeks cannot be explained by differences in OS or PFS. However, it is important as it makes a difference to the cost of pembrolizumab treatment. As the

anticipated licence is for a Q3W regimen, the ERG has used TTD data from the Q3W arm of the KEYNOTE-006 trial in their analysis.

In the ERG's experience TTD is usually l than PFS due to patients stopping due to poor tolerability to a prescribed treatment. This was the case for pembrolizumab in the KEYNOTE-002[39] trial, and for ipilimumab in the KEYNOTE-006 trial. However, in the pembrolizumab Q3W arm of the KEYNOTE-006 trial, some patients continued to receive pembrolizumab treatment after progression, with the TTD K-M data including more patients than the PFS analysis at various points. This was most notable between week 10 and week 24. The reason for this difference is unclear. This does not affect the analysis but raises the issue of how long the drug will be given to patients in clinical practice and whether progression will be a reliable indicator of the time at which treatment is stopped. This is an important factor to consider when trying assessing the long-term cost effectiveness of pembrolizumab in clinical practice in England and Wales.

The ERG modified the company's model so that the pembrolizumab Q3W TTD data were used directly during the first year, followed by projected estimates thereafter (using an exponential distribution). For ipilimumab, TTD data from the KEYNOTE-006 trial were used directly. The ERG notes that there is an isolated case of ipilimumab being used at 12 months. However, given that such use is outside of its licensed indication, the ERG has used the TTD data directly but retained the four cycle limit implemented in the company model.

No TTD data are available (either to the company or the ERG) for the BRAF inhibitors considered in the model and, therefore, in the model, patients who are prescribed these treatments continue on treatment until progression or unacceptable toxicity.

The KEYNOTE-006 PFS and TTD trial data, as well as an exponential trend fitted by the ERG to the TTD data, are displayed in Figure 14.

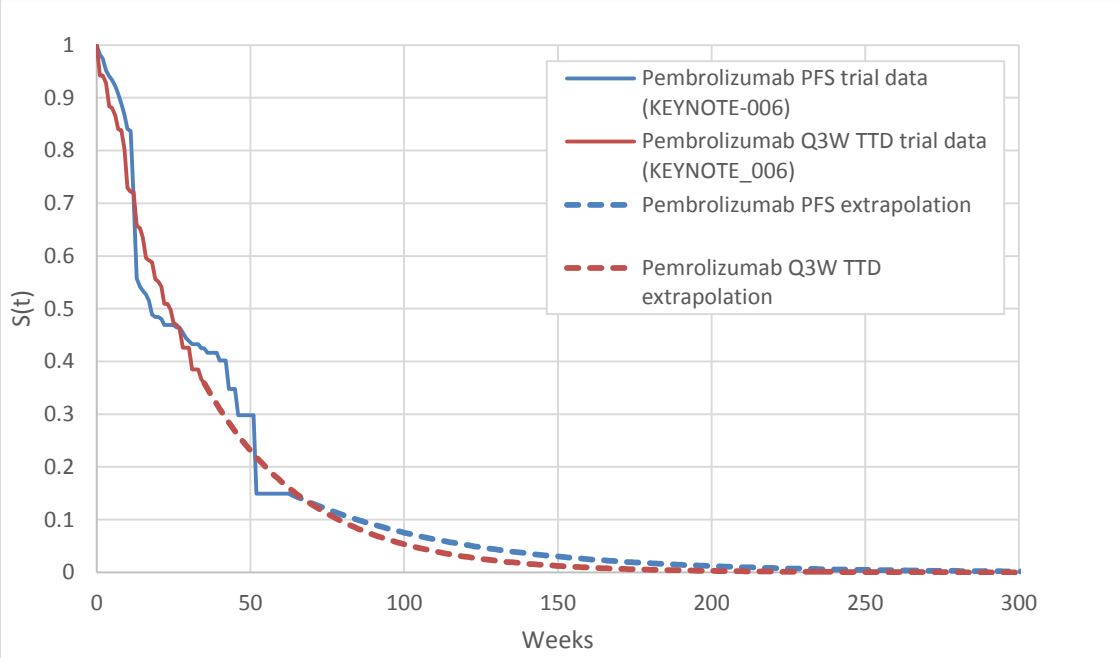


Figure 14 TTD in KEYNOTE-006 with fitted exponential projection model on K-M data compared with pembrolizumab PFS (remodelled by ERG)

The ERG model amendment increases the cost of pembrolizumab treatment by £4,434 per patient and decreases the cost of treatment with ipilimumab by just over £4,284 per patient. So, for a mixed population (i.e. a population of patients with $BRAF^{V600}$ wild-type and positive mutations) this model amendment has no effect on the base case result, i.e. treatment with pembrolizumab continues to dominate treatment with ipilimumab.

For patients with $BRAF^{V600}$ positive mutations, vemurafenib treatment remains dominated by pembrolizumab treatment, whilst the ICER for pembrolizumab versus dabrafenib rises to £10,560 per QALY gained.

6.5 Utility values

Rather than the impact of the changes outlined in Section 6.5.1 and 6.5.2 being presented separately in the results tables (Table 55, Table 56 and Table 57), the ERG's preferred approach is to apply both changes to the company's model.

6.5.1 Non-US (European) utility values

As part of the clarification process, the ERG requested an analysis that separated the utility scores collected during the KEYNOTE-006 trial depending on whether patients were resident in the US. This analysis shows that the non-US subgroup responses are generally more pessimistic than those of patients treated in the US. The effect of using the non-US

(European) utility scores in the company's model is that, for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations, use of non-US utility values decreases the QALY estimates in the pembrolizumab arm by 0.05 QALYs and in the ipilimumab arm by 0.03 QALYs. This change makes no difference to the dominance of pembrolizumab over ipilimumab.

For the population of patients with $BRAF^{V600}$ positive mutations, use of European (non-US) utility estimates decreases the incremental QALY gain of pembrolizumab compared to vemurafenib by 0.03 QALYs which does not alter the dominance of pembrolizumab. When compared with dabrafenib, using European (non-US) utility estimates reduces the QALY gain obtained from pembrolizumab treatment by 0.02 QALYs, increasing the estimated ICER by £92 to £5,944 per QALY gained.

6.5.2 Combined progressive disease state and time to death utilities

The company uses utility data relating to time to death, pooling values from the pembrolizumab Q3W arm and the ipilimumab arm of the KEYNOTE-006 trial. The company included no justification as to why values collected from patients in the pembrolizumab Q2W arm of that trial were not also pooled. To partially address the flaw in the model structure, which means that there is no disbenefit to patients associated with progressive disease (only a reduction in treatment costs), the ERG has used both pre- and post-progression utilities and time to death utilities in the model, with values based upon a pooling of the values collected from all patients (both pembrolizumab and the ipilimumab arms) in the KEYNOTE-006 trial.

The result of incorporating these changes into the model is that, for a mixed population of patients with $BRAF^{V600}$ wild-type and mutation positive patients, use of progression based utility estimates decreases the incremental QALY gain of pembrolizumab over ipilimumab by 0.03 QALYs. However, this has no noticeable effect on the base case cost effectiveness result, with pembrolizumab continuing to dominate ipilimumab.

For vemurafenib, use of progression based utilities results in a fall in incremental QALYs compared to pembrolizumab of 0.2 QALYs. This reduction did not affect the base case result, with pembrolizumab continuing to dominate vemurafenib. For the comparison with dabrafenib, use of progression based utilities resulted in a change in incremental QALYs compared to pembrolizumab of 0.14 QALYs, raising the ICER by £947 to £6,799 per QALY gained.

6.6 Drug dose based on a UK population

The ERG adjusted dosages based on UK values for body weight reported in the Health Survey for England[92] (HSE) 2011 (82.5kg for males and 69.5kg for females), and using a log-normal distribution. This approach results in a small reduction in the total treatment costs for both pembrolizumab and ipilimumab (£169 and £379 per patient respectively) and increases the dominance of pembrolizumab over ipilimumab for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations.

For patients with $BRAF^{V600}$ positive mutations this change increases the dominance of pembrolizumab over vemurafenib and lowers the ICER for pembrolizumab versus dabrafenib by £1,224 to £4,628 per QALY gained.

6.7 ERG's preferred drug administration costs

The ERG used the cost associated with the HRG[93] code for simple chemotherapy ("Deliver simple parenteral chemotherapy at first - day case and regular day/night") when modelling the cost of delivering both pembrolizumab and ipilimumab. The resultant effect was to reduce the cost of ipilimumab treatment for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations) by £237 (0.2%). As such, base case model results are not affected, with pembrolizumab dominant over treatment with ipilimumab for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations.

6.8 Effects of ERG model amendments on cost effectiveness

Table 55, Table 56 and Table 57 summarise the impact of the ERG's amendments to the company's model on the estimated cost effectiveness of pembrolizumab in comparison with ipilimumab, vemurafenib and dabrafenib respectively. Results are presented for individual amendments and then a combined result is estimated encompassing all of the ERG's suggested amendments. The results, after combining all of the ERG's amendments, suggest that pembrolizumab continues to dominate ipilimumab (for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations) and vemurafenib (in a population of patients with $BRAF^{V600}$ positive mutations). The ICER for pembrolizumab compared to dabrafenib in a population with $BRAF^{V600}$ positive mutations rises to £11,077 per QALY gained.

6.8.1 Scenarios

The ERG carried out two scenarios that explored the impact of extending treatment with pembrolizumab and PFS. This was to explore the impact of uncertainty in how long-term PFS and treatment duration may be in reality given the extrapolation is based on only 12

months of data. The scenarios were constructed to 'stress test' the model findings if long-term treatment and PFS had been underestimated by these projections.

Specifically, one scenario assumed that all patients in the PFS state and on treatment at 2 years in the model continue in a PFS state and on pembrolizumab for a further 3 years before progressing according to a constant hazard and ending treatment at the end of that period. A second, more extreme, scenario assumes that treatment and PFS continue for a further 3 years beyond that assumed in the first scenario. After ERG amendments to the model, these two scenarios apply to the approximately 7% of patients who have not progressed and are still on treatment after 2 years.

Under the first scenario, for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations, pembrolizumab remains less expensive than ipilimumab and is dominant. For the second scenario, pembrolizumab becomes more expensive than ipilimumab but remains more effective with an ICER of £11,678 per QALY gained.

For the population of patients with $BRAF^{V600}$ positive mutations, under the first scenario pembrolizumab no longer dominates vemurafenib with an ICER of £2,796 per QALY gained and, in the second scenario, the ICER rises to £13,532 per QALY gained. Comparing treatment with pembrolizumab to dabrafenib, under the first scenario the ICER rises to £21,903 per QALY gained and under the second scenario the ICER rises to £31,242 per QALY gained.

6.9 Comparator patient access schemes

The company's base case includes a PAS discount of [redacted] on the list price of pembrolizumab but zero discount on the cost of any of the comparators. Table 88 in the CS includes potential ICERs per QALY gained for pembrolizumab versus each of the three comparators given a range of simple discount rates (from 0% to 95%).

The ERG has access to the agreed PAS prices for ipilimumab, vemurafenib and dabrafenib and has used these discounts to produce alternative ICERs per QALY gained for the company's base case and for the results generated by the ERG's amendments to the company's model. These results are reported in a separate Appendix to this ERG report.

Once the relevant PAS are applied to all four drugs, pembrolizumab becomes more expensive than all the comparators and no longer dominates any of them in either the company's base case or in any of the ERG's revisions. In all cases, after the ERG's

amendments have been applied, the ICERs for all three comparisons are less than £50,000 per QALY gained.

6.10 Summary of the ERG critique

When each individual ERG amendment to the company model is made the dominant position of pembrolizumab compared to ipilimumab for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations is unaffected. This remains the case even if all of the ERG's changes to the company's model are adopted. In all cases, pembrolizumab continues to cost less and be more effective than ipilimumab.

When considering treatments specific to the population of patients with $BRAF^{V600}$ positive mutations, none of the ERG's model amendments (either singularly or combined) affect the base case position that treatment with vemurafenib is dominated by pembrolizumab, i.e. pembrolizumab continues to cost less and be more effective than vemurafenib. In terms of the comparison with dabrafenib, individually, some of the ERG's amendments do have relatively small effects on the company's cost effectiveness estimates. The largest change occurs when the ERG's preferred method of estimating treatment duration is employed (increasing the ICER by £4,585 per QALY gained). However, when all of the ERG's amendments are implemented together, the company's base case estimate only changes by £16 (from £5,852 to £5,868 per QALY gained).

Table 55 Cost effectiveness results for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations: pembrolizumab versus ipilimumab (PAS included for pembrolizumab at [redacted])

ERG model amendment	Pembrolizumab			Ipilimumab			Incremental			ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£ per QALY gained
Company's base case	**£76,689**	**3.14**	**5.08**	**£97,873**	**2.69**	**4.37**	**-£21,185**	**0.44**	**0.71**	**Dominated**
R1) ERG's preferred OS extrapolation and non-cancer mortality amendment	£80,029	3.61	5.83	£100,887	3.12	5.06	-£20,858	0.49	0.77	Dominated
R2) ERG's preferred (INV based) PFS estimates	£79,131	3.14	5.08	£97,883	2.69	4.37	-£18,752	0.44	0.71	Dominated
R3) Treatment duration based on TTD rather than PFS	£81,123	3.14	5.08	£93,826	2.69	4.37	-£12,703	0.44	0.71	Dominated
R4) Combined progressive disease and time to death utilities (European values)	£76,689	2.57	5.08	£97,873	2.17	4.37	-£21,185	0.40	0.71	Dominated
R5) Drug dose based on a UK population	£75,519	3.14	5.08	£96,494	2.69	4.37	-£20,975	0.44	0.71	Dominated
R6) ERG's preferred drug administration costs	£76,689	3.14	5.08	£97,636	2.69	4.37	-£20,947	0.44	0.71	Dominated
Base case + (R1:R6)	**£83,282**	**2.96**	**5.83**	**£95,315**	**2.52**	**5.06**	**-£12,034**	**0.44**	**0.77**	**Dominated**
Base case + (R1:R6) + Scenario 1	**£92,519**	**2.98**	**5.83**	**£95,315**	**2.52**	**5.06**	**-£2,796**	**0.46**	**0.77**	**Dominated**
Base case + (R1:R6) + Scenario 2	**£100,853**	**3.00**	**5.83**	**£95,315**	**2.52**	**5.06**	**£5,538**	**0.47**	**0.77**	**£11,678**

Costs and QALYs discounted; life years undiscounted
ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; INV=local investigator; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; QALYs=quality adjusted life years

Table 56 Cost effectiveness results for the population of patients with $BRAF^{V600}$ positive mutations: pembrolizumab versus vemurafenib (PAS included for pembrolizumab at [redacted])

ERG model amendment	Pembrolizumab			Vemurafenib			Incremental			ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£ per QALY gained
Company's base case	**£76,689**	**3.14**	**5.08**	**£83,384**	**1.73**	**2.74**	**-£6,695**	**1.40**	**2.34**	**Dominated**
R1) ERG's preferred OS extrapolation and non-cancer	£80,029	3.61	5.83	£90,411	2.72	4.42	-£10,382	0.88	1.42	Dominated
R2) ERG's preferred (INV based) PFS estimates	£79,131	3.14	5.08	£83,384	1.73	2.74	-£4,252	1.40	2.34	Dominated
R3) Treatment duration based on TTD rather than PFS	£81,123	3.14	5.08	£83,384	1.73	2.74	-£2,140	1.40	2.34	Dominated
R4) Combined progressive disease and time to death utilities (European values)	£76,689	2.57	5.08	£83,384	1.42	2.74	-£6,695	1.15	2.34	Dominated
R5) Drug dose based on a UK population	£75,519	3.14	5.08	£83,384	1.73	2.74	-£7,865	1.40	2.34	Dominated
R6) ERG's preferred drug administration costs	-	-	-	-	-	-	-	-	-	-
Base case + (R1:R5)	**£83,282**	**2.96**	**5.83**	**£90,411**	**2.23**	**4.42**	**-£7,130**	**0.73**	**1.42**	**Dominated**
Base case + (R1:R5) + Scenario 1	**£92,519**	**2.98**	**5.83**	**£90,411**	**2.23**	**4.42**	**£2,108**	**0.75**	**1.42**	**£2,796**
Base case + (R1:R5) + Scenario 2	**£100,853**	**3.00**	**5.83**	**£90,411**	**2.23**	**4.42**	**£10,442**	**0.77**	**1.42**	**£13,532**

Costs and QALYs discounted; life years undiscounted
ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; INV=local investigator; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; QALYs=quality adjusted life years

Table 57 Cost effectiveness results for the population of patients with $BRAF^{V600}$ positive mutations: pembrolizumab versus dabrafenib (PAS included for pembrolizumab at [redacted])

ERG model amendment	Pembrolizumab			Dabrafenib			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£ per QALY gained	Change
Company's base case	**£76,689**	**3.14**	**5.08**	**£71,029**	**2.17**	**3.41**	**£5,660**	**0.97**	**1.67**	**£5,852**	
R1) ERG's preferred OS extrapolation and non-cancer	£80,029	3.61	5.83	£74,267	2.63	4.18	£5,762	0.98	1.66	£5,868	£16
R2) ERG's preferred (INV based) PFS estimates	£79,131	3.14	5.08	£71,029	2.17	3.41	£8,103	0.97	1.67	£8,377	£2,525
R3) Treatment duration based on TTD rather than PFS	£81,123	3.14	5.08	£71,029	2.17	3.41	£10,095	0.97	1.67	£10,437	£4,585
R4) Combined progressive disease and time to death utilities (European values)	£76,689	2.57	5.08	£71,029	1.77	3.41	£5,660	0.80	1.67	£7,090	£1,238
R5) Drug dose based on a UK population	£75,519	3.14	5.08	£71,029	2.17	3.41	£4,490	0.97	1.67	£4,628	-£1,224
R6) ERG's preferred drug administration costs	-	-	-	-	-	-	-	-	-	-	-
Base case + (R1:R6)	**£83,282**	**2.96**	**5.83**	**£74,267**	**2.15**	**4.18**	**£9,014**	**0.81**	**1.66**	**£11,077**	**£5,225**
Base case + (R1:R6) + Scenario 1	**£92,519**	**2.98**	**5.83**	**£74,267**	**2.15**	**4.18**	**£18,252**	**0.83**	**1.66**	**£21,903**	**£16,051**
Base case + (R1:R6) + Scenario 2	**£100,853**	**3.00**	**5.83**	**£74,267**	**2.15**	**4.18**	**£26,586**	**0.85**	**1.66**	**£31,242**	**£25,390**

Costs and QALYs discounted; life years undiscounted
ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; INV=local investigator; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; QALYs=quality adjusted life years

7 END OF LIFE

In Section 4.13.2 of the CS, the company puts forward the case that pembrolizumab meets the NICE 'End of Life' criteria.

The NICE criteria for applying a less restrictive assessment of cost effectiveness for 'End of Life' are that:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and
- The treatment is licensed or otherwise indicated, for small patient populations.

The company claims that pembrolizumab meets the NICE 'End of Life' criteria for the reasons set out in Table 58. The ERG agrees that patients with metastatic melanoma have a life expectancy of less than 24 months.

The ERG notes that the anticipated licence for pembrolizumab does not distinguish between lines of treatment. In the CS for this appraisal, the company has estimated that 1304 first-line patients are eligible for treatment with pembrolizumab. In the CS[84] for the appraisal of pembrolizumab following treatment with ipilimumab, the company has estimated that the patient population for second-line treatment is 657. The ERG agrees that pembrolizumab is licensed for a small population.

In terms of life extension, the ERG agrees that pembrolizumab offers a mean OS gain of approximately 4 months when compared with ipilimumab for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations (Appendix 4). For the comparison of pembrolizumab with vemurafenib and dabrafenib for the population of patients with $BRAF^{V600}$ positive mutations, the ERG is uncertain whether pembrolizumab offers a mean extension to life greater than 3 months. This is due to the methodological weaknesses in the method used by the company to compare PFS and OS across the three drugs.

Table 58 Company's 'End of life' criteria

Criterion	Data available
1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS is lower than 24 months: Treatment-naïve patients treated with ipilimumab experience a median OS of 13.5 months, and 11.4 months if they have been previously treated.[86] Median OS for treatment-naïve patients with $BRAF^{V600}$ positive mutations treated is 13.6 months[45] with vemurafenib and 20.1 months for dabrafenib[94]
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	Pembrolizumab offers an extension to life of at least 3 months compared to ipilimumab, vemurafenib and dabrafenib: The average number of life years gained with pembrolizumab as estimated by the economic model is 5.08 years, compared to 4.37 life years with ipilimumab, 3.41 with dabrafenib and 2.74 with vemurafenib
3. The treatment is licensed or otherwise indicated for small patient populations	The estimated number of patients eligible for pembrolizumab in England is expected to be approximately 1,304 patients in 2016 (if approved) - see Table 5 and Sections 3.4 and 6 of CS

Source: CS, Table 64

8 DISCUSSION

8.1 Summary of clinical effectiveness issues

8.1.1 Evidence from the KEYNOTE-006 trial

The company presented clinical evidence from the KEYNOTE-006 trial. The main areas of uncertainty are: i) the absence of mature OS data ii) the impact of the early closure of the trial and iii) the lack of evidence for the efficacy of the anticipated licensed dose of pembrolizumab (2mg/kg Q3W).

i) Absence of mature overall survival data

The available OS data are from IA2 of the KEYNOTE-006 trial, representing only 12 months of patient follow-up. At the time of IA2, median OS had not been reached; however, based on the positive OS results, the trial DMC decided to terminate the trial and allow patients treated with ipilimumab access to treatment with pembrolizumab at disease progression. The ERG notes that the statistical stopping rule was included in the trial analysis plan; however, the early termination of the trial means that the true OS benefit of pembrolizumab may never be known.

ii) Early closure of the trial

The ERG cautions that there is strong evidence that results from trials that are terminated early may overestimate treatment effects, even in the presence of statistical stopping rules.[41,42] This finding is particularly pertinent to trials where there are a small number of events (less than 200). The company considers that the IA2 OS data from the KEYNOTE-006 trial are definitive and no formal analysis will be conducted at the time of the planned final analysis at 21 months follow-up. The EMA has stipulated that the company must provide the final OS results from the KEYNOTE-006 trial and the company anticipates that data analysis will be complete in the second half of 2016. The strength of the evidence submitted in support of treatment with pembrolizumab would be improved if data from the planned final analysis were available, even though these results will inevitably include data contaminated by patient crossover from ipilimumab to pembrolizumab.

iii) Lack of evidence for the anticipated licensed dose

The KEYNOTE-006 trial provides evidence for the efficacy of treatment with pembrolizumab 10mg/kg Q3W compared to treatment with ipilimumab. The KEYNOTE-006 trial data do not provide evidence for the efficacy of the anticipated licensed dose (2mg/kg Q3W). The EMA has considered the data from the KEYNOTE-006 trial, as well as that from a number of additional studies (randomised and non-randomised) in which pembrolizumab has been

used as a treatment, and has concluded that doses of 2mg/kg Q3W and 10mg/kg Q3W are of similar efficacy in a population of patients with advanced melanoma. The ERG is aware that in the studies considered by the EMA, the majority of recruited patients who received the anticipated licensed dose of pembrolizumab (2mg/kg Q3W) had also received previous treatment with ipilimumab. The ERG considers that the available evidence for the equivalence of pembrolizumab 2mg/kg versus 10mg/kg Q3W in the patient population relevant to the present appraisal (i.e. not previously treated with ipilimumab) is limited, but accepts the EMA's decision.

8.1.2 Evidence generated by the network meta-analyses

The company has compared treatment with pembrolizumab to treatment with vemurafenib and dabrafenib using four NMAs. The ERG considers that the NMAs suffer from methodological weakness and that, in the absence of head to head trials, the clinical efficacy of treatment with pembrolizumab compared with treatment with vemurafenib and dabrafenib is unclear. The company does not use the results of these NMAs in their base case cost effectiveness analysis.

8.1.3 Licensed indication

The anticipated licensed indication for pembrolizumab is for the treatment of advanced (unresectable or metastatic) melanoma in adults. Treatment with pembrolizumab will therefore be an option for both patients who have, and have not, received other therapies (including $BRAF^{V600}$ inhibitors and ipilimumab). The ERG is aware that a separate appraisal[33] relevant to patients with advanced melanoma who have received previous treatment with ipilimumab is ongoing.

8.1.4 Length of time treated with pembrolizumab

The patients recruited to the KEYNOTE-006 trial received up to 16 cycles of treatment with pembrolizumab (mean=8). It is unclear whether any limits will be placed on the number of treatments available to patients if pembrolizumab is recommended for use in the NHS. There are no data available to suggest how many treatments might be optimal in clinical practice; the ERG notes that in the original trial protocol it was stated that no more than 24 months of treatment was to be administered to patients.

8.1.5 Available treatment options

The ERG agrees that there are few treatment options available for patients with advanced melanoma and, if the early trial results are borne out in the long-term, pembrolizumab would offer a significant new treatment option for patients with advanced melanoma. Other options

may soon be available for this group of patients. The EMA has recently (April 2015) given a positive opinion to another anti PD-1 agent, nivolumab, as a monotherapy for the treatment of advanced melanoma. NICE's draft scopes for the appraisals of nivolumab for use in advanced melanoma with, and without, a $BRAF^{V600}$ positive mutation, are currently out for consultation.

8.2 Summary of cost effectiveness issues

8.2.1 Model structure

The ERG has concerns regarding the overall structure of the model submitted by the company. The model produces counterintuitive findings in that pembrolizumab becomes increasingly cost effective the more ineffective it is at preventing disease progression.

8.2.2 Limited data

Pembrolizumab and ipilimumab efficacy data have been sourced from the KEYNOTE-006 trial and are only available for 12 months. Efficacy data for vemurafenib and dabrafenib (which have been obtained by digitising published K-M plots) are only available for 60 weeks. Therefore, the period over which results depend on extrapolated estimates is about 29 years. Analysis of the company's base case results shows that nearly 90% of the estimated survival benefit for pembrolizumab compared with ipilimumab occurs within this projected period, meaning that the validity of the projected survival estimates are of crucial importance to the assessment of cost effectiveness.

8.2.3 Survival projection

The ERG has some concerns with the methods used by the company to project PFS and OS (for all treatments). The pembrolizumab and ipilimumab PFS projections rely on the assumption of proportional hazards. Analyses undertaken by the ERG suggest that that assumption does not hold. The company's OS projections for this comparison used some questionable external data that resulted in the morality risk during the second extrapolation phase being implausible (sometimes rates fluctuated erratically and were occasionally zero). In addition these projections also relied on out of date registry data.

The vemurafenib and dabrafenib PFS estimates were not adjusted for differences in patient characteristics and, whilst OS data were adjusted, the ERG considers that the adjustment method employed had serious limitations and therefore results should be considered unreliable. In addition the company's OS projections for these comparisons relied on out of date registry data.

The ERG has carried out exploratory analysis to determine OS (see Appendix 3) and has estimated that the survival benefit associated with pembrolizumab compared with ipilimumab is less than half that estimated by the company (4.1 months compared with 8.6 months).

8.2.4 Costs

Direct treatment costs (drug acquisition and administration) are the most influential costs in the model (for example, over 90% of the overall cost saving of pembrolizumab compared to ipilimumab is attributable to differences in direct treatment costs). This means that, in reality, the only influential variables are treatment costs and length of time on treatment. Treatment costs have already been agreed with the Department of Health, and are therefore fixed, and survival benefit is uncertain.

8.2.5 Cost effectiveness results

Direct treatment costs (drug acquisition and administration) are the most influential costs in the model (for example, over 90% of the overall cost saving of pembrolizumab compared to ipilimumab is attributable to differences in direct treatment costs). This means that, in reality, the only influential variables are treatment costs and length of time on treatment. Treatment costs have already been agreed with the Department of Health, and are therefore fixed, and survival benefit is uncertain.

9 OVERALL CONCLUSIONS

Clinical effectiveness

- There is no phase III RCT evidence to support the use of the anticipated licensed dose of pembrolizumab (2mg/kg Q3W) to treat advanced melanoma in patients previously untreated with ipilimumab in either a first- or second-line setting
- The ERG cautiously accepts the EMA's statement that the 2mg/kg Q3W and 10mg/kg Q3W doses are clinically equivalent for this indication in this population
- Twelve months of data are available from the phase III KEYNOTE-006 trial. These data suggests that pembrolizumab, at a dose of 10mg/kg Q3W, is more effective than ipilimumab and both groups of patients suffer similar levels of AEs. However, this evidence comes from an interim analysis and the trial was stopped early for benefit.

Cost effectiveness

- The design of the company's model leads to counter-intuitive results – pembrolizumab becomes increasingly cost effective the more ineffective it is at preventing disease progression. This is because progression is only linked to lower treatment costs and not to any reduction in quality of life
- The ERG made six amendments to the company's model. These relate to the way in which PFS and OS were modelled, estimation of treatment duration, non-US utility values, using drug doses based on a UK population, and equal administration costs for pembrolizumab and ipilimumab
- The company and the ERG's main cost effectiveness results use the PAS price for pembrolizumab and list prices for the comparator drugs
- For the comparison of pembrolizumab 2mg/kg Q3W in a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations, the company's results show that pembrolizumab dominates ipilimumab (i.e. it is cheaper and delivers more benefit). Results for this comparison were largely robust to the ERG's amendments, even an exploratory OS analysis undertaken by the ERG which reduced the OS benefit for pembrolizumab compared with ipilimumab by over 50%. Only in the scenario where patients continue on pembrolizumab for a significantly longer period than the submitted model predicts, does pembrolizumab lose its dominance over ipilimumab
- For patients with $BRAF^{V600}$ positive mutations, pembrolizumab 2mg/kg Q3W dominates vemurafenib and, compared with dabrafenib, the ICER is £5,852 per QALY gained. Again, these results are largely robust to the ERG's amendments. However, the ERG considers that when pembrolizumab is compared to either vemurafenib or dabrafenib, the ICERs cannot be considered robust as they are based on unreliable survival data.
- Analyses carried out by the ERG using PAS prices for all of the treatments show that after implementing all of the ERG's amendments, the ICERs for pembrolizumab versus all three comparators (ipilimumab, vemurafenib and dabrafenib) are less than £50,000 per QALY.

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11 APPENDICES

11.1 Appendix 1: Description and critique of search strategies for evidence of clinical effectiveness

Clinical effectiveness

Searches were reported for the databases; Medline, Medline in Process, EMBASE, The Cochrane Library (CENTRAL only) and Toxline. The company reported hand searches were undertaken to identify additional studies in the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and Society of Melanoma Research (SMR) and clinicaltrials.gov. The submission did not include details of the search terms used for the hand searching process; therefore the ERG was unable to comment on these searches.

The date of the search and the full date span is included in the report; the searches were well reported. Despite reporting the full strategies, when re-creating the searches the ERG found they required some form of editing, such as inclusion of parenthesis in order for certain search lines to work. The full search strategies included in appendix 2 indicate the search terms included were relevant and included MeSH and free text as well as a simplified RCT filter. The search for CENTRAL did not include free text terms for melanoma. The exclusion of animal studies has been carried out correctly but should have been as a medical subject heading and not as free text.

Indirect treatment and mixed treatment comparison

The company carried out searches for indirect treatment and mixed treatment comparisons on the same databases reported above. The company included the drug comparators; ipilimumab, dacarbazine, vemurafenib and dabrafenib in the strategy. The search carried out for adverse reactions is the same as the search for direct evidence. These searches are reported in the CS (Appendix 7 and 15 respectively).

Cost effectiveness

The company performed a search of the same medical databases to identify published cost-effectiveness analyses and references, the full search strategies are documented in the CS (Appendix 17). The search was performed in July 2014 and updated in March 2015 in the following databases: MEDLINE; MEDLINE in Process; EMBASE; EconLIT, NHSEED. In the cost-effectiveness searches, the reported population terms and drugs names in the database strategies were considered comprehensive by the ERG. A comprehensive economics filter was used in Medline and EMBASE. The searches carried out in NHS EED

and EconLit included only Melanoma search terms, which the ERG deems to be appropriate due to the small numbers retrieved in these databases. Hand searches were also carried out in ASCO, ESMO and ISPOR (limited to the last 2 years).

Measurement and valuation of health effects

Searches were carried out on previous listed databases and were adequate and easily reproducible. The searches included population terms and a HRQOL filter which the ERG considers to be a comprehensive filter. The search for EconLIT was that used for the cost effectiveness search. Hand searches were again carried out in ASCO, ESMO and ISPOR. The search strategies are documented in the CS (Appendix 21).

Resource use and costs searches

The company carried out searches documented in the CS (Appendix 23) to retrieve resource use and cost references. The search included population search terms and a cost use filter. The searches are fully reported including dates and the date spans of the databases.

Summary of searching

Despite some limitations to the search terms and search strategies the ERG concluded that searching was carried out to an adequate standard and accurately reflected the population and indication. The ERG is confident no relevant references have been missed by the company.

11.2 Appendix 2: Adverse events reported from the company NMAs

Table 59 Summary of adverse events from company NMA

Trial	Treatment	Any AE n (%)	Any AE (grade ≥ 3) n (%)	Any discontinuation n (%)	Discontinuation due to AE n (%)	Discontinuation due to disease progression or death n (%)
KEYNOTE-006	Pembrolizumab 10mg/kg Q2W	221 (80)	NR	NR	11 (4)	0
	Pembrolizumab 10mg/kg Q3W	202 (73)	NR	NR	19 (7)	0
	Ipilimumab 3mg/kg Q3W	187 (73)	NR	NR	24 (9)	0
BREAK-3[25]	Dabrafenib 150mg bid	100 (54)	NR	80 (43)	5 (3)	66 (35)
	Dacarbazine 1000mg/m^2 Q3W	26 (44)	NR	46 (73)	2 (3)	5 (8)
BRIM-3[22,45]	Vemurafenib 960 mg bid	NR	NR	NR	24 (7)	0
	Dacarbazine 1000 mg/m^2 Q3W	NR	NR	NR	6 (2)	0
Hersh 2011[43]	Ipilimumab 3mg/kg Q4W	29 (74)	5 (13)	31 (74)	1 (2)	25 (60)
	Dacarbazine 250mg/m^2 5 days/3 weeks+ipilimumab 3mg/kg Q4W	31 (89)	8 (23)	20 (56)	3 (8)	15 (42)
Robert 2011[28]	Dacarbazine 850mg/m^2 Q3W+ipilimumab 10mg/kg weeks 1, 4, 7, and 10	244 (99)	139 (56)	236 (96)	95 (39)	114 (46)
	Dacarbazine 850mg/m^2 Q3W	236 (94)	69 (28)	245 (98)	20 (8)	194 (77)
Hodi 2010[44]	Ipilimumab 3mg/kg Q3W+gp100 Q3W	374 (98)	173 (46)	NR	34 (9)	93 (24)
	Ipilimumab 3mg/kg Q3W	127 (97)	60 (46)	NR	17 (13)	21 (16)
	gp100 Q3W	128 (97)	62 (47)	NR	5 (4)	43 (33)

bid=twice daily; gp100=glycoprotein 100; Q2W=treatment every 2 weeks; Q3W=treatment every 3 weeks; Q4W= treatment every 4 weeks
Source: CS, Appendix Table 4

Table 60 Treatment emergent adverse events from company NMA

Trial	Treatment	Skin-related adverse events			Hematologic adverse events					Gastrointestinal-related adverse events				Liver-related adverse events n (%)	Immune-related (grade ≥ 3) n (%)
		Any n (%)	Pruritus n (%)	Rash n (%)	Neutropenia n (%)	Thrombocytopenia n (%)	Anemia n (%)	>ALT n (%)	> AST n (%)	Colitis-related (grade ≥ 3) n (%)	Diarrhoea n (%)	Nausea n (%)	Vomiting n (%)		
KEYNOTE-006	Pembrolizumab 10mg/kg Q2W	4 (1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0
	Pembrolizumab 1mg/kg Q3W	3 (1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0
	Ipilimumab 3mg/kg Q3W	1 (<1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0
BREAK-3[25]	Dabrafenib 150mg bid	NR	0	0	1 (1)	1 (1)	NR	0	0	NR	0	0	0	0	NR
	Dacarbazine 1000mg/m^2 Q3W	NR	0	0	7 (12)	3 (5)	NR	0	0	NR	0	0	0	0	NR
BRIM-3[22,45]	Vemurafenib 960mg bid	NR	5 (1)	28 (8)	1 (<1)	NR	NR	NR	NR	NR	2 (1)	4 (1)	4 (1)	NR	NR
	Dacarbazine 100 mg/m^2 Q3W	NR	0	0	23 (8)	NR	NR	NR	NR	NR	1 0	5 (2)	3 (1)	NR	NR
Hersh 2011[43]	Ipilimumab 3mg/kg Q4W	19 (49)	0	1 (3)	0	0	NR	NR	NR	NR	0	0	NR	0	NR
	Dacarbazine 250mg/m^2 5 days/3 weeks +ipilimumab 3mg/kg Q4W	15 (43)	0	1 (3)	0	0	NR	NR	NR	NR	0	1 (3)	NR	0	NR
Robert 2011[28]	Dacarbazine 850 mg/m^2 Q3W +ipilimumab 10mg/kg weeks 1, 4, 7, and 10	NR	5 (2)	3 (1)	0	NR	0	54 (22)	45 (18)	NR	10 (4)	4 (2)	8 (3)	0	103 (42)
	Dacarbazine 850mg/m^2 Q3W	NR	0	0	0	NR	0	2 (1)	3 (1)	NR	0	3 (1)	4 (2)	0	15 (6)
Hodi 2010 [44]	Ipilimumab 3mg/kg Q3W+gp100 Q3W	152 (40)	1 (0)	5 (1)	0	0	11 (3)	2 (1)	1 0	12 (3)	17 (4)	6 (2)	7 (2)	4 (1)	39 (10)
	Ipilimumab 3mg/kg Q3W	57 (44)	0	1 (1)	0	0	4 (3)	0	0	7 (5)	7 (5)	3 (2)	3 (2)	0	19 (15)
	gp100 Q3W	22 (17)	NR	NR	0	0	11 (8)	0	0	0	1 (1)	3 (2)	3 (2)	3 (2)	4 (3)

bid=twice daily; gp100=glycoprotein 100; Q2W=treatment every 2 weeks; Q3W=treatment every 3 weeks; Source: CS, Appendix Table 5

11.3 Appendix 3: ERG Revisions to the company's model: pembrolizumab STA (ID801)

All revisions are activated by a binary logic switch with 0=unchanged, 1 (or any non-zero number)=apply ERG modification.

Logic switches are indicated by range variables Mod_n where n = 1 to 10. The Mod numbers do not directly match the Table Row numbers.

A menu of revisions/Mod numbers appears on the 'Results' worksheet together with summary results as used to transfer to the ERG report

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
R1. ERG OS projections and non cancer mortality amendment	Mod_9	ID801_ERG_OS_PFS_TTD_dose_life.xlsx	Paste Worksheet **'ERG_OS'** into model Paste worksheet "**ERG Life Tables**" into model In Sheets 'Pt Flow_Pem', Insert formula in cell **BG15** =IF(Mod_9=1,'ERG OS'!AT11,"-") Copy cell formula in **BG15** to **BG16:BG2104** Replace formula in **H15** =IF(ISNUMBER(BG15),BG15,'Modelled OS'!BC24) Copy cell formula in **H15** to **H16:H2104** In Sheets 'Pt Flow_Ipi', Insert formula in cell **BF15** =IF(Mod_9=1,'ERG OS'!BZ11,"-") Copy cell formula in **BF15** to **BF16:BF2104** Replace formula in **H15** =IF(ISNUMBER(BF15),BF15,'Modelled OS'!CO24) Copy cell formula in **H15** to **H16:H2104** In Sheets 'Pt Flow_Vem', Insert formula in cell **BD15** =IF(Mod_9=1,'ERG OS'!BF11,"-") Copy cell formula in **BD15** to **BD16:BD2104** Replace formula in **H15** =IF(ISNUMBER(BD15),BD15,'Modelled OS'!DD24) Copy cell formula in **H15** to **H16:H2104** In Sheets 'Pt Flow_Dab',

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
			Insert formula in cell **BD15** =IF(Mod_9=1,'ERG OS'!EL11,"-") Copy cell formula in **BD15** to **BD16:BD2104** Replace formula in **H15** =IF(ISNUMBER(BD15),BD15,'Modelled OS'!ED24) Copy cell formula in **H15** to **H16:H2104**
R2. ERG PFS projections	Mod_6-8	ID801_ERG_OS_PFS_TTD_dose_life.xlsx N.B this revision also sets up part of revision scenarios 1 & 2	Paste Worksheet **'ERG_PFS'** into model In Sheets 'Pt Flow_Pem', Insert formula in cell **BF15**=IF(Mod_6=1,'ERG PFS'!$M11,IF(Mod_7=1,'ERG PFS'!$N11,IF(Mod_8=1,'ERG PFS'!$O11,"-"))) Copy cell formula in **BF15** to **BF16:BF2104** Replace formula in **I15** =IF(ISNUMBER(BF15),BF15,'Modelled PFS'!M21) Copy cell formula in **I15** to **I16:I2104** In Sheets 'Pt Flow_Ipi', Insert formula in cell **BE15** =IF(OR(Mod_6=1,Mod_7=1,Mod_8=1),'ERG PFS'!$AB11,"-") Copy cell formula in **BE15** to **BE16:BE2104** Replace formula in **I15** =IF(ISNUMBER(BE15),BE15,'Modelled PFS'!Y21) Copy cell formula in **I15** to **I16:I2104**

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
R3. Treatment duration based on TTD rather than PFS	Mod_3	ID801_ERG_OS_PFS_TTD_dose_life.xlsx N.B this revision also sets up part of revision scenarios 1 & 2	Paste Worksheet **'ERG_ToT'** into model In Sheets 'Pt Flow_Pem', Insert formula in cell **BE15** =IF(Mod_3=1,'ERG ToT'!N11,IF(Mod_4=1,'ERG ToT'!O11,IF(Mod_5=1,'ERG ToT'!P11,"-"))) Copy cell formula in **BE15** to **BE16:BE2104** Replace formula in **AK15** =IF(ISNUMBER(BE15), IF(D15/3=ROUND(D15/3,0),IF(Control.pembro.restrict="Yes",(IF(C15<Control.pembro.restrict.months,G15*BE15*cost_pem,0)),'Pt Flow_Pem'!G15*'Pt Flow_Pem'!BE15*cost_pem_list),0),IF(D15/3=ROUND(D15/3,0),IF(Control.pembro.restrict="Yes",(IF(C15<Control.pembro.restrict.months,G15*P15*cost_pem,0)),'Pt Flow_Pem'!G15*'Pt Flow_Pem'!P15*cost_pem_list),0)*p_treated_pembro) Copy cell formula in **AK15** to **AK16:AK2104** In Sheets 'Pt Flow_Ipi', Insert formula in cell **BD15**=IF(OR(Mod_3=1,Mod_4=1,Mod_5=1),'ERG ToT'!AC11,"-") Copy cell formula in **BD15** to **BD16:BD2104** Replace formula in **AK15** =IF(ISNUMBER(BD15),IF(D15<12,IF($D15/3=ROUND(D15/3,0),BD15*cost_ipi,0)*G15,0),IF(D15<12,IF($D15/3=ROUND(D15/3,0),P15*cost_ipi,0)*G15*IF($D15/3=ROUND(D15/3,0),CHOOSE((D15/3)+1,p_treated_ipi,p_treated_ipi2,p_treated_ipi3,p_treated_ipi4),1),0)) Copy cell formula in **AK15** to **AK16:AK2104**

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
R4. Combined progressive disease and time to death utilities (European values)	Mod_1&2		In sheet 'Control Sheet', change Control_utility_method to "Progression status" In Sheets 'Pt Flow_Pem', 'Pt Flow_Ipi', 'Pt Flow_Vem' and 'Pt Flow_Dab' Replace formula in cell **AJ16** by =IF(Control.utility.method="Time to death","",IF(Mod_1=0,0,BD16*F16)) Copy cell **AJ16** to **AJ17:AJ2104** Insert formula in cell **BD16** =-W16*MIN(D16,13)/13*Utilities!$I$30 Copy cell **BD16** to **BD17:BD2104** In Sheet 'Utilities', create tables for EoL QoL decrement as follows: Insert formula in cell **I25** =(util.12months.pem-util.9.to.12.pem)*90/365.25 Insert formula in cell **I26** =(util.12months.pem-util.6.to.9.pem)*90/365.25 Insert formula in cell **I27** =(util.12months.pem-util.3.to.6.pem)*90/365.25 Insert formula in cell **I28** =(util.12months.pem-util.1.to.3.pem)*60/365.25 Insert formula in cell **I29** =(util.12months.pem-util.1month.pem)*30/365.25 Insert formula in cell **I30** =SUM(I25:I29) Insert formula in cell **J25** =(util.12months.ipi-util.9.to.12.ipi)*90/365.25 Insert formula in cell **J26** =(util.12months. ipi -util.6.to.9. ipi)*90/365.25 Insert formula in cell **J27** =(util.12months. ipi -util.3.to.6. ipi)*90/365.25 Insert formula in cell **J28** =(util.12months. ipi -util.1.to.3. ipi)*60/365.25 Insert formula in cell **J29** =(util.12months. ipi -util.1month. ipi)*30/365.25 Insert formula in cell **J30** =SUM(J25:J29) Insert formula in cell **K25** =(util.12months.vem-util.9.to.12.vem)*90/365.25 Insert formula in cell **K26** =(util.12months.vem-util.6.to.9.pem)*90/365.25 Insert formula in cell **K27** =(util.12months.vem-util.3.to.6.vem)*90/365.25 Insert formula in cell **K28** =(util.12months.vem-util.1.to.3.vem)*60/365.25

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
			Insert formula in cell **K29** =(util.12months.vem-util.1month.vem)*30/365.25 Insert formula in cell **K30** =SUM(K25:K29) Insert formula in cell **L25** =(util.12months.dab-util.9.to.12.dab)*90/365.25 Insert formula in cell **L26** =(util.12months.dab -util.6.to.9.dab)*90/365.25 Insert formula in cell **L27** =(util.12months.dab -util.3.to.6. dab)*90/365.25 Insert formula in cell **L28** =(util.12months. dab -util.1.to.3. dab)*60/365.25 Insert formula in cell **L29** =(util.12months. dab -util.1month. dab)*30/365.25 Insert formula in cell **L30** =SUM(L25:L29) create tables of European EQ-5D values as follows: Cell **V15** =0.808, Cell **V16** =0.696, Cell **V17** = 0.642, Cell **V18** = 0.664, Cell **V19** = 0.563, Cell **V20** = 0.365, Cell **W15** =0.821, Cell **W16** =0.692, Cell **W17** = 0.623, Cell **W18** = 0.656, Cell **W19** = 0.544, Cell **W20** = 0.506, Cell **X15** =0.788, Cell **X16** =0.7, Cell **X17** = 0.673, Cell **X18** = 0.673, Cell **X19** = 0.571, Cell **X20** = 0.107, Cell **N36** = 0.779, Cell **N37** = 0.672, Cell **O36** = 0.793, Cell **O37** = 0.682, Cell **P36** = 0.758, Cell **P37** = 0.66 Insert formula in cell **D24** =IF(Mod_2=0,IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D15,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$H15,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$L15,Utilities!$P15))),IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D15,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$V15,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$W15,Utilities!$X15)))) Copy cell **D24** to cells **E24:G24** Insert formula in cell **D25** =IF(Mod_2=0,IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D16,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$H16,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$L16,Utilities!$P16))),IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D16,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$V16,IF('Control

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
			Sheet'!$D$48=Lists!$K$13,Utilities!$W16,Utilities!$X16)))) Copy cell **D25** to cells **E25:G25** Insert formula in cell **D26** =IF(Mod_2=0,IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D17,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$H17,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$L17,Utilities!$P17))),IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D17,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$V17,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$W17,Utilities!$X17)))) Copy cell **D26** to cells **E26:G26** Insert formula in cell **D27** =IF(Mod_2=0,IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D18,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$H18,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$L18,Utilities!$P18))),IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D18,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$V18,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$W18,Utilities!$X18)))) Copy cell **D27** to cells **E27:G27** Insert formula in cell **D28** =IF(Mod_2=0,IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D19,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$H19,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$L19,Utilities!$P19))),IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D19,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$V19,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$W19,Utilities!$X19)))) Copy cell **D28** to cells **E28:G28** Insert formula in cell **D29** =IF(Mod_2=0,IF('Control

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
			Sheet'!$D$48=Lists!$K$11,Utilities!$D20,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$H20,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$L20,Utilities!$P20))),IF('Control Sheet'!$D$48=Lists!$K$11,Utilities!$D20,IF('Control Sheet'!$D$48=Lists!$K$12,Utilities!$V20,IF('Control Sheet'!$D$48=Lists!$K$13,Utilities!$W20,Utilities!$X20)))) Copy cell **D29** to cells **E29:G29** Insert formula in cell **D43** =IF(Mod_2=0,IF('Control Sheet'!$D$53=Utilities!$E$34,Utilities!$D36,IF('Control Sheet'!$D$53=Utilities!$G$34,Utilities!$F36,IF('Control Sheet'!$D$53=Utilities!$I$34,Utilities!$H36,Utilities!$J36))),IF('Control Sheet'!$D$53=Utilities!$E$34,Utilities!$D36,IF('Control Sheet'!$D$53=Utilities!$N$34,Utilities!$N36,IF('Control Sheet'!$D$53=Utilities!$O$34,Utilities!$O36,Utilities!$P36)))) Copy formula in cell **D43** to cells **D43:G44**
R5. Drug dose based on a UK population	Mod_10	ID801_ERG_OS_PFS_TTD_dose_life.xlsx	Paste Worksheet **'ERG_Dosing** into model Insert formula in cell **E36** =IF(Mod_10=1,H28,SUMPRODUCT($C$28:$C$34,E28:E34)) Copy cell formula in **E36** to **F36** Insert formula in cell **H28** ='ERG drug costs'!N9 Insert formula in cell **I28** ='ERG drug costs'!Z9
R6. ERG's preferred drug administration costs	N/A		In sheet 'Drug Costs', change cells D72 and D74 to "Deliver simple parenteral chemotherapy at first - day case and regular day/night

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
Scenario 1	Mod_4&7	ID801_ERG_OS_PFS_TTD_dose_life.xlsx N.B this revision also sets up revisions R2 and R3, and scenario 2	Create alternative PFS projections: Paste Worksheet **'ERG_PFS'** into model In Sheets 'Pt Flow_Pem', Insert formula in cell **BF15**=IF(Mod_6=1,'ERG PFS'!$M11,IF(Mod_7=1,'ERG PFS'!$N11,IF(Mod_8=1,'ERG PFS'!$O11,"-"))) Copy cell formula in **BF15** to **BF16:BF2104** Replace formula in **I15** =IF(ISNUMBER(BF15),BF15,'Modelled PFS'!M21) Copy cell formula in **I15** to **I16:I2104** In Sheets 'Pt Flow_Ipi', Insert formula in cell **BE15** =IF(OR(Mod_6=1,Mod_7=1,Mod_8=1),'ERG PFS'!$AB11,"-") Copy cell formula in **BE15** to **BE16:BE2104** Replace formula in **I15** =IF(ISNUMBER(BE15),BE15,'Modelled PFS'!Y21) Copy cell formula in **I15** to **I16:I2104** Create alternative time on time to treatment discontinuation projections: Paste Worksheet **'ERG_ToT'** into model In Sheets 'Pt Flow_Pem', Insert formula in cell **BE15** =IF(Mod_3=1,'ERG ToT'!N11,IF(Mod_4=1,'ERG ToT'!O11,IF(Mod_5=1,'ERG ToT'!P11,"-")))

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
			Copy cell formula in **BE15** to **BE16:BE2104** Replace formula in **AK15** =IF(ISNUMBER(BE15), IF(D15/3=ROUND(D15/3,0),IF(Control.pembro.restrict="Yes",(IF(C15<Control.pembro.restrict.months,G15*BE15*cost_pem,0)),'Pt Flow_Pem'!G15*'Pt Flow_Pem'!BE15*cost_pem_list),0),IF(D15/3=ROUND(D15/3,0),IF(Control.pembro.restrict="Yes",(IF(C15<Control.pembro.restrict.months,G15*P15*cost_pem,0)),'Pt Flow_Pem'!G15*'Pt Flow_Pem'!P15*cost_pem_list),0)*p_treated_pembro) Copy cell formula in **AK15** to **AK16:AK2104** In Sheets 'Pt Flow_Ipi', Insert formula in cell **BD15**=IF(OR(Mod_3=1,Mod_4=1,Mod_5=1),'ERG ToT'!AC11,"-") Copy cell formula in **BD15** to **BD16:BD2104** Replace formula in **AK15** =IF(ISNUMBER(BD15),IF(D15<12,IF($D15/3=ROUND(D15/3,0),BD15*cost_ipi,0)*G15,0),IF(D15<12,IF($D15/3=ROUND(D15/3,0),P15*cost_ipi,0)*G15*IF($D15/3=ROUND(D15/3,0),CHOOSE((D15/3)+1,p_treated_ipi,p_treated_ipi2,p_treated_ipi3,p_treated_ipi4),1),0)) Copy cell formula in **AK15** to **AK16:AK2104**

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
Scenario 2	Mod_5&8	ID801_ERG_OS_PFS_TTD_dose_life.xlsx N.B this revision also sets up revisions R2 and R3, and scenario 1	Create alternative PFS projections: Paste Worksheet **'ERG_PFS'** into model In Sheets 'Pt Flow_Pem', Insert formula in cell **BF15**=IF(Mod_6=1,'ERG PFS'!$M11,IF(Mod_7=1,'ERG PFS'!$N11,IF(Mod_8=1,'ERG PFS'!$O11,"-"))) Copy cell formula in **BF15** to **BF16:BF2104** Replace formula in **I15** =IF(ISNUMBER(BF15),BF15,'Modelled PFS'!M21) Copy cell formula in **I15** to **I16:I2104** In Sheets 'Pt Flow_Ipi', Insert formula in cell **BE15** =IF(OR(Mod_6=1,Mod_7=1,Mod_8=1),'ERG PFS'!$AB11,"-") Copy cell formula in **BE15** to **BE16:BE2104** Replace formula in **I15** =IF(ISNUMBER(BE15),BE15,'Modelled PFS'!Y21) Copy cell formula in **I15** to **I16:I2104** Create alternative time on time to treatment discontinuation projections: Paste Worksheet **'ERG_ToT'** into model In Sheets 'Pt Flow_Pem', Insert formula in cell **BE15** =IF(Mod_3=1,'ERG ToT'!N11,IF(Mod_4=1,'ERG ToT'!O11,IF(Mod_5=1,'ERG ToT'!P11,"-")))

ERG Section 6 results table revision	Binary switch	Associated detail	Implementation instructions
			Copy cell formula in **BE15** to **BE16:BE2104** Replace formula in **AK15** =IF(ISNUMBER(BE15), IF(D15/3=ROUND(D15/3,0),IF(Control.pembro.restrict="Yes",(IF(C15<Control.pembro.restrict.months,G15*BE15*cost_pem,0)),'Pt Flow_Pem'!G15*'Pt Flow_Pem'!BE15*cost_pem_list),0),IF(D15/3=ROUND(D15/3,0),IF(Control.pembro.restrict="Yes",(IF(C15<Control.pembro.restrict.months,G15*P15*cost_pem,0)),'Pt Flow_Pem'!G15*'Pt Flow_Pem'!P15*cost_pem_list),0)*p_treated_pembro) Copy cell formula in **AK15** to **AK16:AK2104** In Sheets 'Pt Flow_Ipi', Insert formula in cell **BD15**=IF(OR(Mod_3=1,Mod_4=1,Mod_5=1),'ERG ToT'!AC11,"-") Copy cell formula in **BD15** to **BD16:BD2104** Replace formula in **AK15** =IF(ISNUMBER(BD15),IF(D15<12,IF($D15/3=ROUND(D15/3,0),BD15*cost_ipi,0)*G15,0),IF(D15<12,IF($D15/3=ROUND(D15/3,0),P15*cost_ipi,0)*G15*IF($D15/3=ROUND(D15/3,0),CHOOSE((D15/3)+1,p_treated_ipi,p_treated_ipi2,p_treated_ipi3,p_treated_ipi4),1),0)) Copy cell formula in **AK15** to **AK16:AK2104**

29 July 2015

11.1 Appendix 4: ERG's alternative estimation of overall survival gain

Examination of the KEYNOTE-006 K-M data indicates that, during the trial, mortality hazard passed through three phases (Figure 15). First, there was a short initial period in which a common (very low) death rate was experienced in both trial arms. Second, during the next phase lasting several months, patients in both trial arms suffered increased mortality rates with more patients dying in the ipilimumab arm than in the pembrolizumab arm. In the third (long-term) phase all patients experienced a common hazard rate equivalent to the rate applicable to the second phase in the pembrolizumab arm. In the second and third phases, the hazard appears to be consistently constant for the duration of the study (equivalent to simple exponential survival functions).

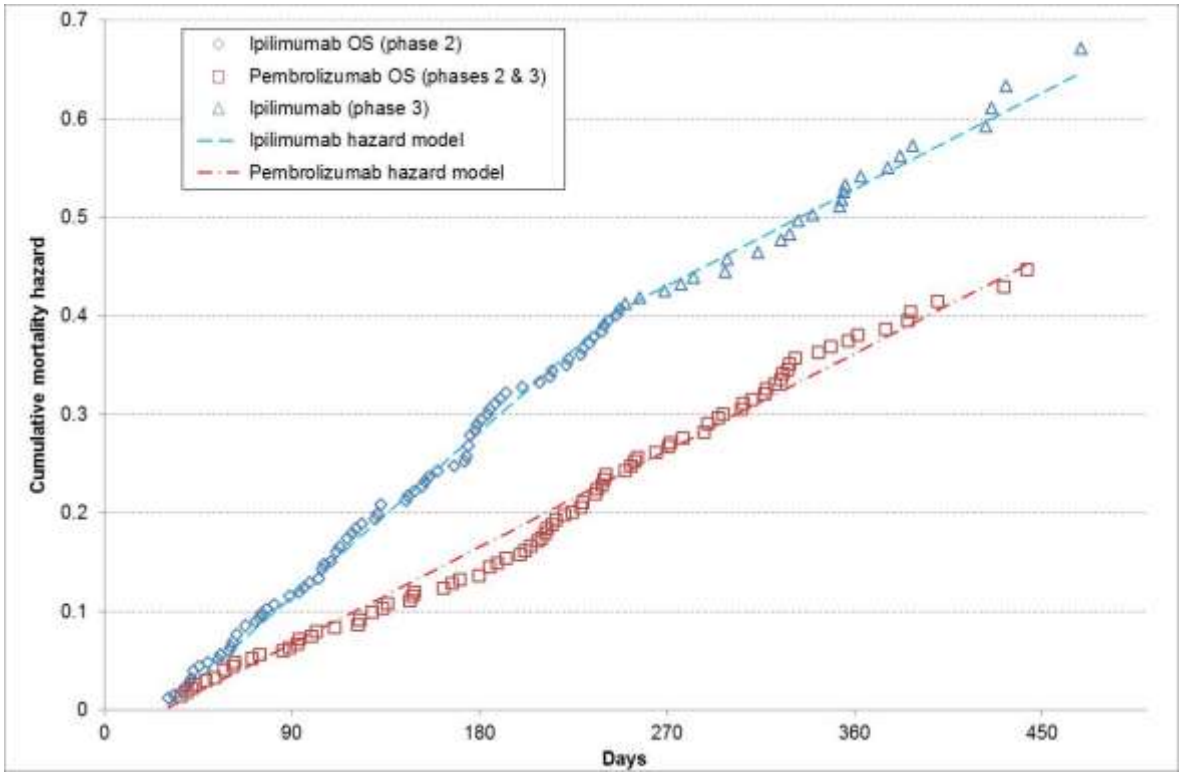

Figure 15 Cumulative mortality hazard trends in KEYNOTE-006 Kaplan-Meier data, illustrating intermediate and long-term hazard models

This analysis of the available evidence suggests a hypothesis in which the mode of action of the two treatments may be compared. During the initial period (about 28 days) a similar small number of deaths occur in each arm to patients whose imminent death could not be predicted by applying the trial exclusion criteria. Thereafter increased mortality risk was resumed in both arms but at different rates. Finally, the mortality rate in the ipilimumab arm reduced to the same level as in the pembrolizumab arm. This would be consistent with a scenario in which the pembrolizumab treatment effect on mortality is established rapidly and sustained throughout the rest of the observed period, whereas the treatment effect of

ipilimumab takes several months (about 8 months) to become fully established, but in the long-term achieves a similar efficacy to that seen in the pembrolizumab arm.

The ERG has applied a method of survival estimation used previously in other NICE technology appraisals – TA309[13] (pemetrexed for non-squamous non-cell lung cancer) and TA269[15] (vemurafenib for treating malignant melanoma). In such situations it is possible to make an accurate estimate of OS gain without requiring specification of any particular parametric survival function, provided it can be assumed that in the long-term surviving patients experience the same pattern of mortality.

The method of calculation is illustrated in Figure 16, and involves applying a time shift of 153 days to the comparator arm data in order to align accurately the final phase of both survival curves, so that the final phase survival estimates are equivalent and make no net contribution to the incremental survival calculation. The AUC method is used to estimate survival in each trial arm. In Figure 16, the horizontal line *BD* indicates the OS proportion at which the shifted ipilimumab curve converges to match the pembrolizumab curve. The AUC beyond the corresponding time points (greater than C for ipilimumab, and greater than E for pembrolizumab) are then identical and so do not contribute to the difference in estimated OS. Thus the OS gain due to pembrolizumab can be easily calculated as the difference in the areas defined by points *A*, *B* and *C* (ipilimumab) and *A*, *D* and *E* (pembrolizumab) as follows:

OS gain = AUC (*ADE*) – AUC (*ABC*)

= 333.7 days – 245.9 days = 125.8 days or 4.13 months

This method depends only upon the final phase of the two survival curves following a common trend, but no assumption is needed as to the particular form of that trend (i.e. it is independent of any assumed survival function).

Using this method the OS gain from use of pembrolizumab rather than ipilimumab is estimated as 126 days (4.1 months), less than half that estimated in the company's base case scenario (8.6 months). It is noted that this change would reduce the QALY gain of pembrolizumab over ipilimumab, although a gain for pembrolizumab would still exist. As ipilimumab would still be more costly than pembrolizumab, pembrolizumab would still dominate ipilimumab. The ERG considers that even with this decrement in OS benefit, treatment with pembrolizumab is likely to dominate ipilimumab.

The ERG cannot say what difference this change would make to the relative cost effectiveness compared to the BRAF inhibitors as we do not have reliable comparable OS data between pembrolizumab and them.

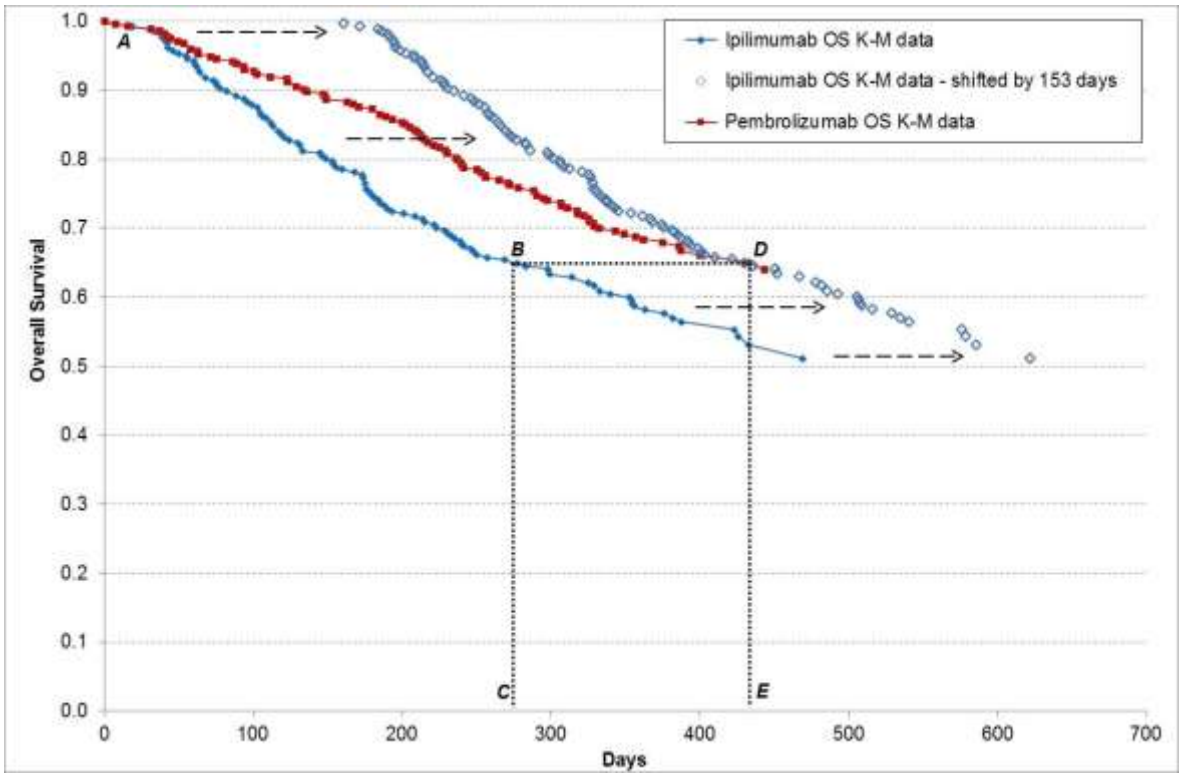

Figure 16 Time-shifting comparator arm of the KEYNOTE-006 trial to allow estimation of OS gain due to use of pembrolizumab

Unfortunately, this approach to estimating OS does not lend itself easily to incorporation into the existing company model without radical redesign, which is beyond the remit of the ERG. However, in principle it is clear that a much simpler robust decision model could be constructed on the basis of the available evidence, avoiding much of the speculative survival modelling currently incorporated in the company model.

Issue 1 Licenced indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 7 “Pembrolizumab is not currently licenced for use in patients with advanced melanoma in Europe”. Page 22 “Pembrolizumab does not currently have a licence in Europe for patients with advanced (unresectable and metastatic) melanoma.	Please note that the European Commission has already issued their decision to approve Keytruda (2 mg/kg administered IV over 30 min every 3 weeks). The signed decision was received on 21st July 2015. As a result, Keytruda is now approved for use in the 28 EU member states, as well as European Economic Area members, Iceland, Liechtenstein and Norway, with the following indication: “KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults” This was communicated to NICE on 22nd July 2015.	To provide further clarification on this point.	Ok, text amended.

Issue 2 Reporting of HRQoL as part of the economic section

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 8 “EuroQol (EQ-5D) data and EORTC-QLQ-C30 data were collected […] the findings are not reported in the clinical effectiveness section of the CS, even though they were used in the base case cost effectiveness analysis.”	The results concerning HRQoL exploratory endpoints are currently unavailable in the KEYNOTE-006 clinical study report (CSR) based on the data reported from the interim analyses 1 and 2 (see page 90 of the CS). Statistical analyses to estimate utilities derived from the KEYNOTE-006 EQ-5D data were conducted for the purposes of this submission.	To provide further clarification on this point.	OK, text amended.

Page 70 “HRQoL data were collected as part of the KEYNOTE-006 trial; the analyses are not reported in the clinical section of the CS”.	The results of these analyses were presented as part of the economic section (section 5.4) since the estimation of utilities was not part of the analyses pre-established in the protocol but were additionally conducted to provide relevant data to reflect NICE’s reference case.		

Issue 3 Minor text correction relating to the ERG critique of the network meta-analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 65 “In view of the extensive heterogeneity within this body of evidence, The ERG does not consider that any reliable estimates of survival effectiveness are possible between pembrolizumab and either vemurafenib”	Add: “and dabrafenib.”	To implement minor text correction.	Ok, text amended.

Issue 4 NICE reference case checklist

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 74, under ‘Type of economic evaluation’ / ‘Does the de novo economic evaluation match the reference case?’ the stated answer is “Cost-effectiveness analysis”	Substitute “Cost-effectiveness analysis” with “Yes”	We conducted a cost-utility analysis and full incremental analyses were reported per subpopulation according to BRAF mutation status.	Ok, text amended.

Issue 5 Drummond checklist

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 75, questions 'Was a well-defined question posed in answerable form?' and 'Was a comprehensive description of the competing alternatives given?'	Substitute "Partially" with "Yes"	The statements provided to justify a 'partial' score seem to be related to the use of clinical evidence and therefore not to the definition of the question or the description of the comparators. Detailed information on the question posed and the comparators considered was presented in section 5.2.	Ok, text amended.

Issue 6 Health-related quality of life

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 80-81 "The company made this design choice as an analysis showed that, in terms of mean utility, there was very little difference between the score associated with PFS and that associated with progressed disease (0.74 and 0.68 respectively)."	We made this design choice because in KEYNOTE-006 the utility data collected post-progression was based on one measurement occurring 30 days after progression, which may not have fully captured the decrease in quality of life as patients get closer to death.	To reflect the reason not to use progression-based utilities in the base case analysis.	Ok, text amended.

Issue 7 Administration costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 83 “The company therefore, considers that pembrolizumab is ‘simple’ to deliver whilst ipilimumab is ‘complex’.” Section 5.10, page 103.	According to the Reference costs guidance for 2013-14 (see: https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2013-to-2014): ▪ Simple parenteral chemotherapy is identified as that with an ‘Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle’. ▪ Complex parenteral chemotherapy is identified as that requiring an ‘Overall time of 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle. In terms of administration times: ▪ The duration of administration of pembrolizumab is 30 minutes per infusion. ▪ Ipilimumab is given as an infusion into a vein over 90 minutes (based on its SmPC). Therefore, different administration codes apply to pembrolizumab and ipilimumab according to the duration of administration of each of these treatments based on the NHS Reference Costs.	To provide further clarification on this point.	Ok, text amended. Not a factual error.

Issue 8 Minor text correction relating to health state unit costs and resource use

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 83 “These data have	Modify to read: “These data […] of ipilimumab	To implement minor text correction.	Ok, text amended.

previously been used in the model considered in an appraisal of the use of ipilimumab for previously treated advanced (unresectable or metastatic melanoma (TA319)."	for previously untreated advanced (unresectable or metastatic melanoma (TA319)."		

Issue 9 Minor text correction to PFS model parameters

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 101 "The ERG therefore considers that the OS projections for vemurafenib and dabrafenib must be considered unreliable."	Modify to read: "The ERG therefore considers that the PFS projections for […]."?	To implement minor text correction.	Ok, text amended.

Issue 10 Combined progressive disease and time to death utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 113 "The company uses utility data relating to time to death, pooling values from the pembrolizumab Q3W arm and the ipilimumab arm of the KEYNOTE-006 trial. The company included no justification as to why values collected from patients in the pembrolizumab Q2W arm of that trial were not also pooled."	In the estimation of utilities based on KEYNOTE-006 EQ-5D data the focus was on the pembrolizumab 10mg/kg Q3W and the ipilimumab arms since these were the arms used for the estimation of the efficacy estimates (PFS and OS) and we wanted to keep consistency between patient populations used for efficacy and QoL estimates.	To provide further clarification on this point.	Ok, text deleted. Not a factual error.

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Merck Sharp & Dohme has submitted clinical and economic evidence to NICE in support of the use of pembrolizumab (Keytruda) for the treatment of advanced melanoma previously untreated with ipilimumab.

Pembrolizumab is licensed in Europe for the treatment of advanced (unresectable or metastatic) melanoma in adults. The marketing authorisation for pembrolizumab was granted by the European Medicines Agency (EMA) on 21st July 2015.

At the time of the submission of this ERG report (29th July 2015), the ERG was unaware that the EMA had issued a final marketing authorisation for pembrolizumab. Hence, throughout this ERG report, the ERG has referred to the *anticipated* licence for pembrolizumab.

1.2 Critique of the decision problem in the company submission

The NICE scope and the company's decision problem for this appraisal address only a subgroup of the population covered by the anticipated licence for pembrolizumab, namely patients with advanced melanoma previously untreated with ipilimumab. A second subpopulation, patients with advanced melanoma who have received treatment with ipilimumab, is being addressed in a separate STA appraisal. Pembrolizumab can be used to treat both a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations and those with $BRAF^{V600}$ positive mutations.

The anticipated pembrolizumab licence is expected to be for a dose of 2mg/kg administered every 3 weeks (Q3W). However, in the pivotal trial (KEYNOTE-006) discussed in the company submission (CS), patients were treated with pembrolizumab at a dose of 10mg/kg Q3W (or 10mg/kg every 2 weeks [Q2W]). There is no direct evidence that allows a comparison of the clinical effectiveness of the 2mg/kg Q3W and the 10mg/kg Q3W doses in patients previously untreated with ipilimumab. The draft European Public Assessment Report (EPAR) issued by the CHMP states that the CHMP has accepted that no differences in the efficacy of 2mg/kg and 10mg/kg are to be expected. The ERG cautiously accepts that the 2mg/kg Q3W and 10mg/kg Q3W doses of pembrolizumab are clinically equivalent when used to treat advanced melanoma in a patient population not previously treated with ipilimumab.

The comparators identified in the NICE scope are ipilimumab, vemurafenib, dabrafenib and dacarbazine. The company has used direct evidence from the KEYNOTE-006 trial to support the clinical effectiveness of pembrolizumab versus ipilimumab. The company has used indirect evidence, generated by conducting a series of network meta-analyses (NMAs), to compare the efficacy of pembrolizumab with all of the comparators specified in the NICE scope. Although included as a comparator in the NMAs, the company does not consider dacarbazine to be a relevant comparator to pembrolizumab; the ERG agrees with this approach.

Clinical evidence is reported in the CS for all five outcomes specified in the NICE scope: overall survival (OS), progression-free survival (PFS), response rate (reported as overall response rate [ORR] and disease control rate), adverse events (AEs) of treatment and health-related quality of life (HRQoL). The ERG notes that the KEYNOTE-006 trial was stopped early for benefit at the second interim analysis (IA2) on the recommendation of the Data Monitoring Committee (DMC) and the data currently available from the trial are immature. EuroQol (EQ-5D) data and EORTC-QLQ-C30 data were collected during the KEYNOTE-006 trial.

The economic analyses addressed by the decision problem match those specified in the NICE scope.

1.3 Summary of clinical effectiveness evidence submitted by the company

Direct evidence

The company carried out a systematic search of the literature and identified one randomised controlled trial (RCT), KEYNOTE-006, which compares pembrolizumab (10mg/kg Q3W) with a relevant comparator (ipilimumab). A dose-escalating RCT, KEYNOTE-001 (Part D) and a non-randomised study (KEYNOTE-001 [Part B1]) were additionally identified as providing supportive evidence for the clinical effectiveness of the anticipated licensed dose (2mg/kg Q3W) of pembrolizumab. .

The KEYNOTE-006 trial included patients with $BRAF^{V600}$ wild-type mutations and those with $BRAF^{V600}$ positive mutations. None of the 834 patients in the trial had been previously treated with ipilimumab. However, around 30% of patients had received at least one line of prior systemic therapy.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

This section summarises the decision problem described by the company in the CS in relation to the final scope[32] issued by NICE. A summary comparison between the final scope[32] and the CS is presented in Table 1. Each parameter in Table 1 is discussed in more detail in the text following the table.

Table 1 NICE scope and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission
Population	People with advanced (unresectable stage III or stage IV) melanoma previously untreated with ipilimumab	As per the NICE scope
Intervention	Pembrolizumab	Pembrolizumab
Comparator(s)	Dacarbazine Ipilimumab Vemurafenib (for people with $BRAF^{V600}$ mutation-positive disease) Dabrafenib (for people with $BRAF^{V600}$ mutation-positive disease)	As per the NICE scope except that the company does not consider dacarbazine to be a relevant comparator
Outcomes	The outcome measures to be considered include: PFS OS RR AEs HRQoL	As per the NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the comparator technologies should be taken into account.	Cost effectiveness is expressed in terms of an incremental cost per QALY. The time horizon considered is 30 years. Costs are considered from an NHS perspective. A range of potential PAS discounts for ipilimumab, vemurafenib and dabrafenib (in 5% increments) is considered as part of the analyses to reflect the confidential PAS prices in place
Subgroups to be considered	None	None
Other considerations	None	None

AE=adverse event; BSC=best supportive care; RR=response rate; OS=overall survival; PAS=patient access schemes; PFS=progression-free survival; QALY=quality adjusted life year. Source: CS, Table 1

3.1 Population

Pembrolizumab is approved for use in Europe. Pembrolizumab, as a monotherapy, is indicated for the treatment of patients with advanced (unresectable and metastatic) melanoma.

arms of the BREAK-3[25] and BRIM-3[22,45] trials than patients in the control arm of the Hodi[44] trial. Considerable differences were also observed with regards to the proportions of males, M1c stage patients, and elevated LDH levels. The ERG has summarised these important differences in Table 31.

Table 31 Patient characteristics in the control arms of the Hodi, BRIM-3 and BREAK-3 trials

Characteristic	Trial (arm)		
	Hodi[44] (gp100)	BRIM-3[22] (dacarbazine)	BREAK-3[22,25] (dacarbazine)
Age (mean)	57.4	52	50
Males	54%	54%	63%
ECOG score of 1 or more	49%	32%	25%
M1c stage	73%	65%	63%
LDH>ULN	38%	58%	30%

ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; ULN=upper limit of normal

In view of the extensive heterogeneity within this body of evidence, the ERG does not consider that any reliable estimates of survival effectiveness are possible between pembrolizumab and either vemurafenib or dabrafenib.

Methodology

In order to implement the results of NMA in the context of non-proportional hazards, the company has applied a complex analytical method (fractional polynomial modelling of hazard ratios) aimed at better reflecting variations in hazard ratios over time in the component trials of the evidence network. The true test of the appropriateness of applying such a technique to the evidence available for this appraisal is to compare the estimated hazard ratios with those available directly from the trials.

Figure 2 indicates that the fractional polynomial method fails to reflect the wide variations in the hazard ratio of pembrolizumab vs ipilimumab seen in the KEYNOTE-006 trial, and results in a trend close to a constant non-varying level (CS, Table 42 Scenario 3b). In particular, the estimated hazard ratio at the end of the observation period is clearly below the hazard ratio actually occurring in the trial. If these values are used to populate the long-term phase of the decision model the result is likely to be a much greater long-term survival advantage for pembrolizumab versus ipilimumab than is consistent with the available evidence from the KEYNOTE-006 trial giving the only direct evidence for these two agents. This leads the ERG to conclude that the NMA results based on the fractional polynomial method cannot be considered a reliable method for estimating the long-term relative

4.12 Conclusions of the clinical effectiveness section

The clinical effectiveness evidence presented in the CS meets the criteria specified in the final scope issued by NICE.[32]

Direct evidence: pembrolizumab vs ipilimumab

- The key source of evidence used by the company to demonstrate the clinical effectiveness of pembrolizumab 2mg/kg Q3W when used to treat advanced melanoma in patients previously untreated with ipilimumab in a first- or second- line setting is the KEYNOTE-006 trial. Pembrolizumab can be used to treat patients with $BRAF^{V600}$ wild-type mutations as well as those with $BRAF^{V600}$ positive mutations

- The KEYNOTE-006 trial does not include a 2mg/kg Q3W arm. The company therefore assumes that pembrolizumab 2mg/kg Q3W and pembrolizumab 10mg/kg Q3W are clinically equivalent

- Results from the KEYNOTE-006 trial show that, compared to treatment with ipilimumab, pembrolizumab 10mg/kg Q3W statistically significantly improves both PFS and OS

- None of the subgroup analyses carried out on data collected during the KEYNOTE-006 trial reveal any statistically significant differences in outcomes between treatments

- Adverse event rates in the KEYNOTE-006 trial are high for all patients. There are no statistically significant differences in AEs between patients in the pembrolizumab arms compared to those in the ipilimumab arm of the trial

- HRQoL data were collected as part of the KEYNOTE-006 trial; results are presented as part of the economics section.

Indirect evidence: pembrolizumab vs ipilimumab, vemurafenib and dabrafenib

- The company reports the results of four NMAs which were carried out to compare treatment with pembrolizumab with ipilimumab, vemurafenib and dabrafenib treatment using a method based on fractional polynomials. Dacarbazine was included in the NMAs but was not considered as a relevant comparator

- In the first-line setting, the results of the NMAs show that treatment with pembrolizumab 10mg/kg Q3W may statistically significantly improve PFS (at 3, 6 and 12 months) and OS (at 6 and 12 months, but not at 18 months) compared to treatment with ipilimumab

- In the second-line setting, there is no statistically significant difference in PFS or OS when comparing treatment with pembrolizumab 10mg/kg Q3W with ipilimumab treatment

- For patients with BRAF positive mutations, when comparing treatment with pembrolizumab 10mg/kg Q3W with vemurafenib treatment, the credibility of the results is questionable as the RPSFT method may not have adequately adjusted for patient crossover

associated with the treatment of advanced melanoma. The ERG considers these details to be very helpful.

5.3 Overview of company's economic modelling

5.3.1 NICE reference case checklist

Table 35 NICE Reference case checklist completed by ERG

Attribute	Reference case[60]	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope[32] developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Patient related direct health effects are considered. No impact on carers has been considered in the model
Perspective on costs	NHS and PSS	Partial. The model only includes NHS costs. Personal Social Service costs have not been considered
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 30 year time horizon
Synthesis of evidence on health effects	Based on systematic review	No – data have primarily been taken from a single clinical trial
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs and the EQ-5D instrument has been used to collect HRQoL data
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes - HRQoL data were collected as part of the KEYNOTE-006 trial
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes - NHS costs, valued at relevant prices, have been used. PSS costs are not included in the model
Discounting	The same annual rate for both costs and effects (currently 3.5%)	Benefits and costs have been discounted at the 3.5% rate

HRQoL=health-related quality of life; PSS=Personal and Social Services; QALY=quality adjusted life year

5.3.2 Drummond checklist

Table 36 Critical appraisal checklist for the economic analysis completed by ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	The company compares pembrolizumab 2mg/kg Q3W versus comparators; however, the only relevant RCT data available are from the use of pembrolizumab 10mg/kg Q3W
Was a comprehensive description of the competing alternatives given?	Yes	Vemurafenib and dabrafenib were described in the CS; however, the indirect methodology used to compare pembrolizumab with these treatments is not clear from the CS or from the submitted model
Was the effectiveness of the programme or services established?	Yes	The ERG had to cautiously accept the EMA's statement that 2mg/kg Q3W and 10mg/kg Q3W doses of pembrolizumab were clinically equivalent as the clinical trial evidence used to inform the submitted model was based on data derived from KEYNOTE-006 (10mg/kg Q3W)
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Partially	The ERG revised the following parameter estimates in the company's model: OS, PFS, TTD, utility values, drug doses and drug administration costs
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic and probabilistic sensitivity analyses were undertaken
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

CS=company submission; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation

5.3.3 Description of company's economic model

A schematic of the company's submitted economic model is provided in the CS and is reproduced in Figure 3. The company's model compares pembrolizumab with ipilimumab, vemurafenib and dabrafenib. The company's cost effectiveness model is a partitioned survival model which comprises three mutually exclusive health states: pre-progression (i.e. progression-free survival [PFS]), post-progression survival (PPS) and death. All patients enter the model in the pre-progression state. At the beginning of each time period patients can either remain in the same health state or progress to a worse health state, i.e. patients in the pre-progression state can either move to the post-progression state or the death

prospects as that observed for patients treated with ipilimumab. The company indicates that they consider this to be a conservative assumption.

Vemurafenib and dabrafenib

First, K-M data from the BRIM-3[45] (vemurafenib) and BREAK-3[25] (dabrafenib) trials are adjusted using the Korn[64] registry algorithm to account for the difference in baseline characteristics between these trials and KEYNOTE-006. These adjusted K-M data are then used to model OS for 60 weeks. Three monthly risks of death from the vemurafenib STA submission (TA319[13]) are used to model survival in both the vemurafenib and dabrafenib arms from 61 to 100 weeks, 101 to 152 weeks and 153 to 200 weeks. Melanoma-specific mortality data (Balch 2001[62]) combined with background mortality data[63] are then used from 201 weeks onwards.

5.3.8 Health-related quality of life

Health-related quality of life data, using the EQ-5D 3L[65] tool, were collected as part of the KEYNOTE-006 trial, at eight different time points, with only one of those time points being after progression (approximately 30 days after the last dose of study drug or before the initiation of a new antineoplastic treatment, whichever came first). Data from the full analysis set (FAS) population (first interim analysis [data cut-off date: 3rd September 2014]) were analysed. Approximately 20% of cases were missing at baseline and approximately 35% were missing at the time of the analysis. Only completed records were included in the analysis. The UK time trade-off (TTO) value set[66] was used to calculate utility values.

In the base case scenario time to death utilities were the pooled values from the 10mg/kg Q3W pembrolizumab arm and the ipilimumab arm. This choice was justified based on the fact that there was no statistically significant difference in quality of life between these two arms.

HRQoL was age-adjusted using the annual utility decrement of 0.0039 that has been calculated based on figures from Kind.[67] Based on the baseline age of patients included in the KEYNOTE-006 trial, this decrement was applied annually from the age of 60 to 75 years to reflect the natural decrease in utility associated with increasing age.

The utility values used in the company's model are based on time to death rather than disease status (i.e. progression free or progressed). The company made this design choice because in KEYNOTE-006 the utility data collected post-progression were based on one measurement occurring 30 days after progression, which may not have fully captured the

decrease in quality of life as patients get closer to death.

Patient EQ-5D scores collected during six time periods were used to estimate the mean utility associated with each period. In the base case, the analyses for each of the time periods relating to time to death less than 360 days used data that were associated with a known death date. However, for the category of 360 or more days to death all patients, including censored patients, were included in the analysis.

Table 40 Mean EQ-5D utility scores by time to death

Time to death (days)	Mean (pooled)	95% CI
≥360*	0.82	0.79 to 0.84
[270, 360)	0.71	0.63 to 0.79
[180,270)	0.66	0.60 to 0.72
[90, 180)	0.66	0.60 to 0.71
[30, 90)	0.57	0.49 to 0.65
<30	0.33	0.11 to 0.55

*This group also includes patients who did not die within the trial and report EQ-5D at any time
Source: CS, Table 77 and Appendix 20 (Table 4)

The company carried out a systematic review to identify studies reporting HRQoL for patients with advanced melanoma. As no studies assessing patients who were naïve to treatment with ipilimumab before entering the study were identified, the search was widened to include patients with advanced melanoma. Eleven studies[68-78] were identified. However, only one paper[73] collected data using the EQ-5D tool from a UK population with advanced melanoma. The company considers that, overall, the utilities derived from the KEYNOTE-006[79] trial are comparable to those found in other trial based studies.

5.3.9 Disutility associated with adverse events

It has been assumed by the company that any impact of AEs on HRQoL has been captured within the EQ-5D scores obtained from the KEYNOTE-006 trial and no further decrement has been applied. The company considers that this is a conservative assumption as pembrolizumab has a favourable AE profile in comparison to ipilimumab, vemurafenib and dabrafenib.

Table 41 Treatment cost per vial/pack

Treatment	Pack/vial details	Cost per pack/vial	Source
Pembrolizumab	50mg vial	[redacted]	Pending confirmation from Department of Health
Ipilimumab	10ml (50mg) vial	£3,750	MIMS 2015[80]
	40ml (200mg) vial	£15,000	
Vemurafenib	240mg 56-tab pack	£1,750	MIMS 2015[80]
Dabrafenib	50 mg, 28-cap pack	£933.33	MIMS 2015[80]
	75 mg, 28-cap pack	£1,400	

Source: CS, Table 81

Table 42 Proportion of patients receiving expected dose

Treatment	Proportion receiving expected dose	Source
Pembrolizumab	87.7%	KEYNOTE-006
Ipilimumab – dose 1	100.0%	KEYNOTE-006
Ipilimumab – dose 2	96.0%	KEYNOTE-006
Ipilimumab – dose 3	86.6%	KEYNOTE-006
Ipilimumab – dose 4	81.3%	KEYNOTE-006
Vemurafenib	100.0%	Assumption
Dabrafenib	100.0%	Assumption

Source: CS, Table 80

Administration costs

Drug administration costs have been sourced from NHS reference costs[81] and are shown in Table 43. Other costs relating to the administration of drugs are displayed in Table 44.

The company notes that the administration time for pembrolizumab is 30 minutes, whilst that for ipilimumab is 90 minutes. In addition, on each occasion before ipilimumab is administered, patients are required to receive liver and thyroid function tests. The company therefore, considers that pembrolizumab is 'simple' to deliver whilst ipilimumab is 'complex'; this is in line with the duration of administration of each of the treatments based on NHS Reference Costs.[81]

The company model assumes that a month's supply of the oral chemotherapies (vemurafenib or dabrafenib) is initially provided in an outpatient setting (Deliver exclusively oral chemotherapy [SB11Z]). Subsequent doses are assumed to be taken at home with repeat prescriptions' collected from the hospital (no appointments required). It is assumed that it will take a hospital pharmacist 12 minutes to check and dispense each prescription.

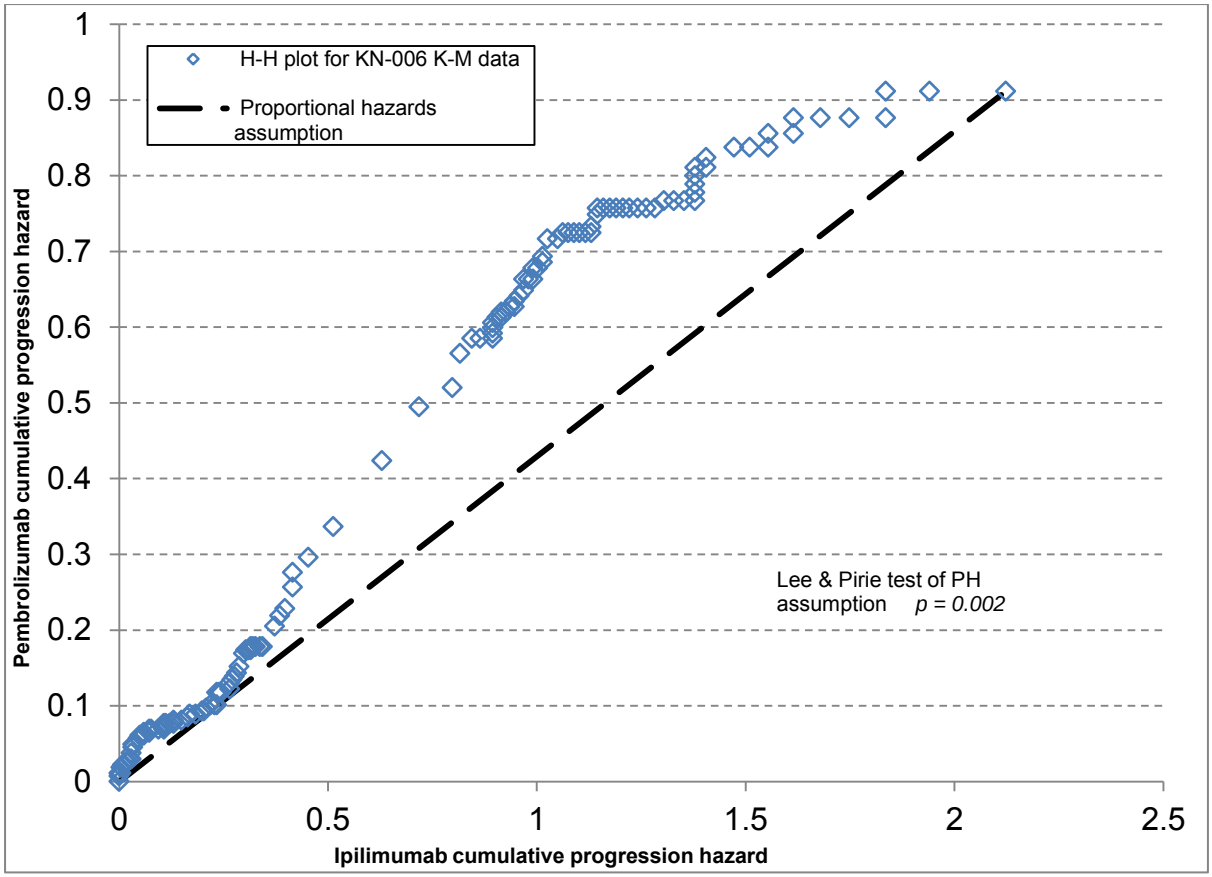

Figure 11 Cumulative mortality hazard plot of KEYNOTE-006 trial arms showing that the assumption that the PFS hazards are proportional is invalid

Pembrolizumab versus vemurafenib and dabrafenib (patients with BRAF^{V600} positive mutations)

For the comparison of pembrolizumab versus vemurafenib and dabrafenib, PFS was estimated using data obtained by digitising published PFS K-M plots from the BRIM-3[22,45] and BREAK-3[25] trials up to 39 weeks, and then using the monthly risk of progression from a recent NICE appraisal which assessed treatment with ipilimumab (TA319[13]). No adjustments have been made for differences in patient characteristics and/or relative treatment effects between the BRIM-3,[22,45] BREAK-3[25] and KEYNOTE-006 trials. The ERG therefore considers that the PFS projections for vemurafenib and dabrafenib must be considered unreliable.

5.7 Model parameters: treatment duration (a mixed population of patients with BRAF^{V600} wild-type and positive mutations)

The company's model uses PFS from the KEYNOTE-006 trial as the basis for costing pembrolizumab and ipilimumab treatment; treatment for patients receiving ipilimumab is limited to 12 weeks. In the ERG's experience, using PFS as a proxy for time to treatment

(European) utility scores in the company's model is that, for a mixed population of patients with $BRAF^{V600}$ wild-type and positive mutations, use of non-US utility values decreases the QALY estimates in the pembrolizumab arm by 0.05 QALYs and in the ipilimumab arm by 0.03 QALYs. This change makes no difference to the dominance of pembrolizumab over ipilimumab.

For the population of patients with $BRAF^{V600}$ positive mutations, use of European (non-US) utility estimates decreases the incremental QALY gain of pembrolizumab compared to vemurafenib by 0.03 QALYs which does not alter the dominance of pembrolizumab. When compared with dabrafenib, using European (non-US) utility estimates reduces the QALY gain obtained from pembrolizumab treatment by 0.02 QALYs, increasing the estimated ICER by £92 to £5,944 per QALY gained.

6.5.2 Combined progressive disease state and time to death utilities

The company uses utility data relating to time to death, pooling values from the pembrolizumab Q3W arm and the ipilimumab arm of the KEYNOTE-006 trial.

To partially address the flaw in the model structure, which means that there is no disbenefit to patients associated with progressive disease (only a reduction in treatment costs), the ERG has used both pre- and post-progression utilities and time to death utilities in the model, with values based upon a pooling of the values collected from all patients (both pembrolizumab and the ipilimumab arms) in the KEYNOTE-006 trial.

The result of incorporating these changes into the model is that, for a mixed population of patients with $BRAF^{V600}$ wild-type and mutation positive patients, use of progression based utility estimates decreases the incremental QALY gain of pembrolizumab over ipilimumab by 0.03 QALYs. However, this has no noticeable effect on the base case cost effectiveness result, with pembrolizumab continuing to dominate ipilimumab.

For vemurafenib, use of progression based utilities results in a fall in incremental QALYs compared to pembrolizumab of 0.2 QALYs. This reduction did not affect the base case result, with pembrolizumab continuing to dominate vemurafenib. For the comparison with dabrafenib, use of progression based utilities resulted in a change in incremental QALYs compared to pembrolizumab of 0.14 QALYs, raising the ICER by £947 to £6,799 per QALY gained.