NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab [ID760]

Merck Sharp & Dohme: Evidence submission

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PEMBROLIZUMAB FOR TREATING UNRESECTABLE, METASTATIC MELANOMA AFTER PROGRESSION WITH IPILIMUMAB [ID760] **1**

MERCK SHARP & DOHME: EVIDENCE SUBMISSION **1**

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ABBREVIATIONS:

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
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CSR	Clinical Study Report
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
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
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EORTC-QLQC30	European Organisation for Research and Treatment Cancer Quality of Life Questionnaire
EQ-5D	EuroQoL 5 Dimensions
FAS	Full-analysis set
FDA	Food and Drug Administration
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
INV	Investigator evaluation
IO	Immuno-oncology
IRO	Integrated radiology and oncology analysis (central review)

IRC	independent review committee
IA2	Second Interim-Analysis
INV	Investigator evaluation
IPCW	Inverse probability of censoring weighted
irAEs	Immune-related AEs
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
MEK	
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
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
STA	Single Technology Appraisal
TIC	Treatment of Investigator choice
TNM	Tumour, Node, and Metastases
TTO	Time Trade Off
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,[1;2] 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.[3]

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 1st line treatment with either a BRAF inhibitor or with ipilimumab. For patient with $BRAF^{V600}$ wild type status, ipilimumab is currently a recommended 1st 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.[4-7] The immuno-oncology (IO) agent, ipilimumab, has a marked benefit for a small proportion of patients,[8], whether $BRAF^{V600}$ mutation positive or wild type, although with a high immune-related AE[9;10] profile. Consequently most patients continue to face a remarkably poor prognosis.[4-6]

The positioning of pembrolizumab in the treatment pathway, following disease progression with ipilimumab and if $BRAF^{V600}$ mutation positive, a BRAF or MEK inhibitor, reflects a step change in the management of patients with unresectable or metastatic melanoma. Patients in this position have no further treatment options, other than palliation (best supportive care [BSC] +/- older chemotherapeutic agents, such as dacarbazine).

1.1 Statement of decision problem

The decision problem addressed in the submission is presented in the below Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with advanced (unresectable stage III or stage IV) melanoma whose disease has progressed after previous treatment with ipilimumab	Adults with unresectable or metastatic melanoma who have progressed after being previously treated with ipilimumab and, if $BRAF^{V600}$ mutation positive, a BRAF or MEK inhibitor	As per the population of interest addressed in the key clinical trials supporting this submission, $BRAF^{V600}$ mutation positive patients must have had a prior treatment regimen with an approved BRAF and/or MEK inhibitor. It is anticipated that the product label may not mandate prior therapy with a BRAF or MEK inhibitor for patients who are $BRAF^{V600}$ mutation positive.
Intervention	Pembrolizumab	Pembrolizumab	In line with NICE final scope
Comparator (s)	• Dacarbazine • Vemurafenib (for people with $BRAF^{V600}$ mutation-positive disease) • Dabrafenib (for people with $BRAF^{V600}$ mutation-positive disease) • BSC	• BSC (including dacarbazine)	Merck Sharp & Dohme Ltd. (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.[11] • 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.[12] • 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 [13] failed to demonstrate

			any benefit with lenolidamide chemotherapy treatment in terms of tumour response, time to progression, or overall survival. The anticipated licence indication for pembrolizumab is "*for the treatment of unresectable or metastatic melanoma in adults"*. Presently it is uncertain whether our final label will mandate prior therapy with a BRAF or MEK inhibitor for patients who are $BRAF^{V600}$ mutation positive. However as our submission is focused on the sub-population of 'patients who have received prior treatment with ipilimumab and if $BRAF^{V600}$ mutation positive, a BRAF or MEK inhibitor', this precludes BRAF inhibitors from being appropriate comparators to pembrolizumab in the population of interest covered within this STA.
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 (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	• 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	In line with NICE final scope

	into account.		
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	A licence for pembrolizumab in the UK is currently pending
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 who have been previously treated with ipilimumab and, if $BRAF^{V600}$ mutation positive, a BRAF or MEK inhibitor. *NB: The above indication covers a sub-population of the anticipated licence indication (KEYTRUDA is indicated for the treatment of unresectable or metastatic melanoma in adults).*
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), with a licence anticipated in July 2015. The anticipated licence indication is "for the treatment of unresectable or metastatic melanoma in adults" whereas our submission is focused on the sub-population of "patients who have received prior treatment with ipilimumab and if $BRAF^{V600}$ mutation positive, a BRAF or MEK inhibitor". Presently it is uncertain whether our final label will mandate prior therapy with a BRAF or MEK inhibitor for patients who are $BRAF^{V600}$ mutation positive.

The route of administration for pembrolizumab is IV infusion, over a 30 minute period. The anticipated licensed dosage will be 2 mg/kg Q3W. Treatment with pembrolizumab continues until disease progression 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

The evidence presented here demonstrates that pembrolizumab provides a valuable treatment option for patients who, having progressed after receipt of the other NICE recommended treatments, have a significant unmet need.

The second interim-analysis (IA2) of KEYNOTE-002, which is a three-arm randomised controlled trial (RCT) comparing pembrolizumab 2 mg/kg Q3W, pembrolizumab 10 mg/kg Q3W and investigator-choice chemotherapy, provides the main evidence base for this submission. Supportive clinical evidence is provided from the randomised 'Part B2' of KEYNOTE-001, which compared two strengths of pembrolizumab (2 mg/kg Q3W and 10 mg/kg Q3W) in the same patient population (ipilimumab-refractory) as that considered in KEYNOTE-002, 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.

A limitation of the evidence base is that long term data is not currently available; results are presented from IA2 of KEYNOTE-002, which provides follow up of between 14 and 16 months for PFS and OS respectively. Additionally, at the point of data analysis for IA2 of KEYNOTE-002, a high proportion (48%) of patients had crossed over from the investigator-choice chemotherapy control arm, to receive pembrolizumab. Despite this, there was a numeric trend in favour of pembrolizumab, and using appropriate statistical modelling approaches to adjust for the high levels of crossover observed in the chemotherapy control arm, a better estimate of the survival benefit of pembrolizumab versus chemotherapy has been presented. In terms of PFS, results from IA2 of KEYNOTE-002 show that treatment with pembrolizumab 2 mg/kg Q3W resulted in a statistically significant improvement relative to chemotherapy control, in patients with ipilimumab-refractory advanced melanoma (hazard ratio = 0.57 [p = <0.0001]). Demonstrated improvement in PFS associated with pembrolizumab is supported by a greater than 4-fold increase in objective response rate and a longer duration of responses compared to chemotherapy (see section 4.7).

Based on previous evidence with immunotherapies, it is likely that median PFS results from KEYNOTE-002 underestimate the potential magnitude of the PFS improvement associated with pembrolizumab. The median time point coincided with the first scheduled scan (which occurred after 12 weeks in both study arms). However from this time point onwards, there is a clear and dramatic separation in PFS curves which persists at 6 and 9 months, as reflected by a 6-month PFS rate of 34.3% in the pembrolizumab 2 mg/kg arm compared to 15.6% in the chemotherapy control arm, and a 9-month PFS rate of 23.7% in the pembrolizumab 2 mg/kg arm compared to 8.0% in the chemotherapy control arm.

Important supportive data concerning the beneficial survival profile associated with pembrolizumab comes from the recently published KEYNOTE-006 study,[14] which compared two dosing regimens of pembrolizumab with ipilimumab in an ipilimumab-naïve population.

Although from an earlier point in the treatment pathway than that in this submission, interim results from KEYNOTE-006 demonstrate a significant improvement in both PFS and OS for pembrolizumab relative to ipilimumab (see section 4.7).

The safety profile of pembrolizumab, when administered at 2 mg/kg Q3W, is favourable when compared to chemotherapy. The mean duration of study treatment in KEYNOTE-002 was nearly 2-fold longer on pembrolizumab compared to chemotherapy, and crude percentages of adverse events (AEs) are therefore likely to underestimate the differences in safety in favour of the control arm. Despite this, drug-related Grade 3-5 AEs were numerically higher in the chemotherapy control arm. The overall frequency of AEs that are potentially immune-related was low (16.3% in the pembrolizumab 2 mg/kg arm). Immune-related AEs were typically Grade 1-2 in severity, and were generally reversible with treatment discontinuation and use of corticosteroids. In the context of ipilimumab which is another type of immunotherapy for melanoma, pembrolizumab compares favourably to ipilimumab from a safety perspective, especially in light of the longer duration on study therapy (see section 4.13).

In both KEYNOTE-001 and KEYNOTE-002, pembrolizumab has been assessed at two different dosages: 2 mg/kg and 10 mg/kg. Results demonstrate that safety and efficacy are comparable between both doses. Clinical efficacy results for pembrolizumab presented in this submission focus on the anticipated licence dose of 2 mg/kg, with results including the 10 mg/kg dosage arm provided as an appendix (Appendix 6).

MSD has consulted extensively on the role of dacarbazine and the other older chemotherapeutic agents and the consensus is that they should be considered in the position of palliation as part of BSC, supported by the fact that dacarbazine is mostly used in a palliative setting outside of clinical trials.[11] Published evidence[12] has demonstrated that chemotherapy is unlikely to have any survival benefit over BSC in patients with advanced metastatic melanoma, with no RCTs demonstrating any improvement in survival with dacarbazine relative to BSC / any other control agent.[11] Consequently the chemotherapy control comparator arm of KEYNOTE-002 could be considered an appropriate proxy for BSC in this treatment setting (see section 4.10.4).

Based on the evidence presented in this submission, pembrolizumab, a novel IO agent with a demonstrated survival benefit, provides a valuable new treatment option for a population in which there is significant unmet need.

1.4 Summary of the cost-effectiveness analysis

Cost-effectiveness of pembrolizumab compared to BSC for the treatment of patients with metastatic or unresectable melanoma previously treated with ipilimumab and if $BRAF^{V600}$ positive mutation, a BRAF inhibitor, was demonstrated through the development of a three-state partitioned survival model. This model considered PFS, post-progression and death), in line with previous HTAs concerning oncology treatments and, more specifically, concerning advanced melanoma (see section 5.2).[1;2;15;16] The model estimated health outcomes (i.e. OS and PFS as a proxy for time spent on treatment) for patients and costs. Quality-adjusted life years (QALYs) were estimated by using time-to-death utilities, in line with previous NICE submissions.[2] Clinical and economic outcomes were projected over a 30-year time horizon to reflect the lifetime of the target population.

The main clinical evidence used to populate the model was the KEYNOTE-002. Since OS data was immature it has been extrapolated and as it was affected by crossover, various crossover adjustment methods were implemented, with the 2-stage adjustment found to be the more appropriate (see sections 1.3, 4.7 and 5.3.2). The median OS estimated for chemotherapy after these adjustments was consistent with what would be expected for chemotherapy OS based on external sources (see sections 5.3.2 and 5.3.3). OS for the pembrolizumab treatment arm was, conservatively, assumed to be similar in the long term to that observed for ipilimumab in the 2nd line setting [8] (see section 5.3.3).This assumption was supported by similar PFS and OS results observed for pembrolizumab from the KEYNOTE-002 trial compared to those from ipilimumab as second-line therapy from the MDX010-020 trial (TA268).[1]. The approach was validated by melanoma clinical experts and supported by the preliminary results of the Phase III, KEYNOTE-006 RCT. In order to project the outcomes of chemotherapy in the long- term, the results of the 2-stage adjustment were used. In sensitivity analyses, alternative scenarios were modelled for both pembrolizumab and chemotherapy making use of alternative crossover adjustments and data sources external to the KEYNOTE-002 trial.

Section 5 details the development of a de novo economic model for pembrolizumab, with Table 1.4.1 below presenting the results. Pembrolizumab increases the life expectancy of patients in 1.59 years, which corresponds to a gain of 1.19 QALYS. In the base case analysis, the ICER is £42,923 (PAS included).

Table 3: Incremental cost-effectiveness results (with PAS)

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (
BSC	£15,960	1.510	1.074	-	-	-	-
Pembrolizumab	£66,955	3.102	2.262	£50,995	1.592	1.188	£42,923
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, for whom recommended effective treatment options have been exhausted. Pembrolizumab significantly improves PFS, and also has been shown to extend OS compared with conventional chemotherapy. Pembrolizumab is a cost-effective therapeutic option when compared to BSC (including conventional chemotherapy) as shown by the results of the de novo cost-effectiveness model. A positive NICE recommendation for pembrolizumab, for the treatment of advanced melanoma in patients who have progressed following treatment with ipilimumab, and if $BRAF^{V600}$ mutation positive, a BRAF or MEK inhibitor, would 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

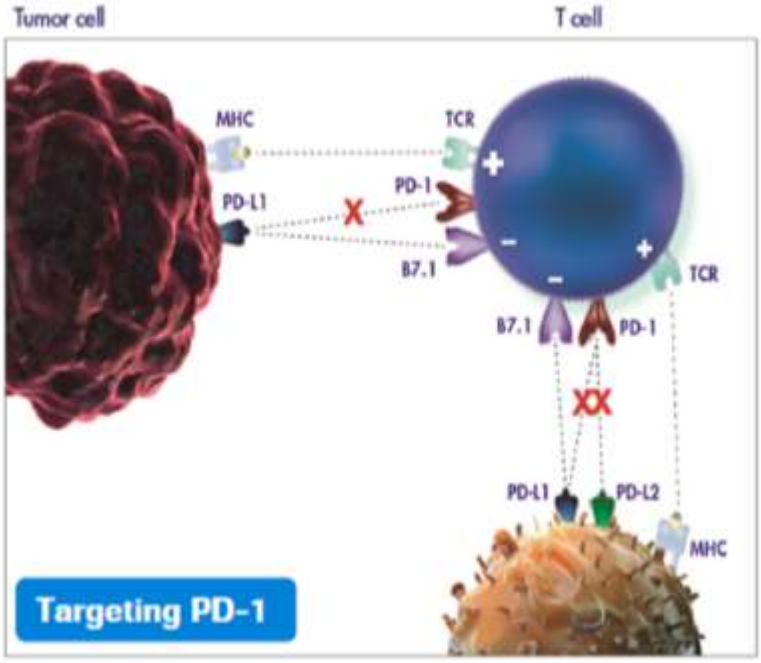
Therapeutic class: Anticipated BNF Category "Other immunomodulating drugs" (08.02.04).[17]

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.[18] The PD-1 ligands, PD-L1 and PD-L2, are frequently upregulated on the surface of many tumour cell surfaces.[19]

Pembrolizumab (Keytruda®) is a potent and highly selective humanised monoclonal antibody (mAb) of the IgG4/kappa isotype.[18] 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).

Figure 1: Pembrolizumab – mode of action



2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1: Current UK regulatory status

- Application submitted: June 2014
- CHMP Opinion due May 2015
- Estimated date of Marketing Authorization: July 2015

2.2.2: Anticipated indication in the UK

The anticipated licence indication in the UK is 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 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.

2.2.6: Summary of the main issues discussed by the regulatory authorities

Not applicable – public assessment report currently unavailable

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

In Israel 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

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

2.3 Administration and costs of the technology

Table 4: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Powder for concentrate for solution for infusion	Draft SmPC (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 (see Appendix 1)
Doses	Induction dose: 2mg/kg every 3 weeks	Draft SmPC (see Appendix 1)
Dosing frequency	Induction: 2mg/kg every 3 weeks until disease progression or unacceptable toxicities	Draft SmPC (see Appendix 1)
Average length of a course of treatment	Mean PFS for a patient randomised onto pembrolizumab in the KEYNOTE-002 clinical trial is estimated at approximately 6.86 cycles (20.57 weeks)	Clinical trial – CSR KEYNOTE-002[20]
Average cost of a course of treatment	Based on a mean PFS of 6.86 cycles the average cost per cycle is £1,315.	Average length of a course based on clinical trial – KEYNOTE-002
Anticipated average interval between courses of treatments	Treatment regimen is continuous until disease progression or unacceptable toxicity leading to discontinuation	CSR KEYNOTE-002[20]
Anticipated number of repeat courses of treatments	Repeated treatment is not anticipated	Draft SmPC (see Appendix 1)
Dose adjustments	No dose adjustment is expected	Draft SmPC (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 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 (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,[1;2] vemurafenib[21] and dabrafenib[16].

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 extending up to 10 years in some patients[8]. 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.[22]

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.[4;23-30]

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.[31]

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 to 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).[32]

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),[33] 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).

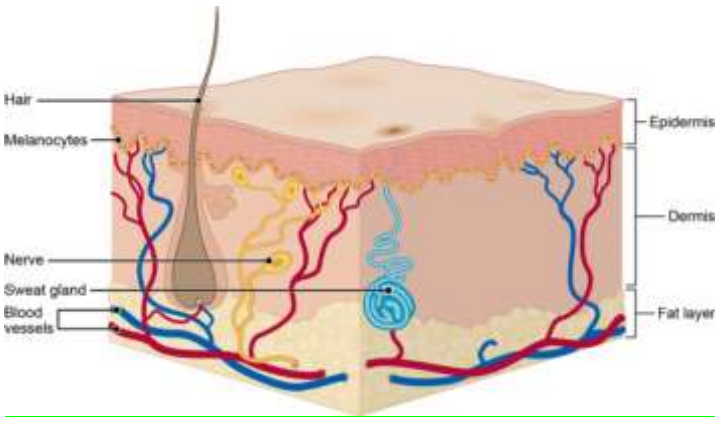
3 Health condition and position of the technology in the treatment pathway

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.[1;34]

Figure 2: The structure of the skin. [Adapted from Cancer Research UK (2014a)] .{Cancer Research UK, 2015 112 /id;National Institute for Health and Care Excellence (NICE), 2012 79 /id}



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).{Cancer Research UK, 2015 112 /id;National Institute for Health and Care Excellence (NICE), 2012 79 /id}

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.{Cancer Research UK, 2015 112 /id;Erdei, 2010 41 /id;Maio, 2012 46 /id;National Institute for Health and Care Excellence (NICE), 2012 79 /id}

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.[35] 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%.[36]

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.[37;38] 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.[39]

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.[39]

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).[40]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.[41-45] Although differences in emotional distress do not seem to differ by stage of melanoma, women report greater distress than men.[46] Increased levels of impairment have been associated with poor recovery, an increase in morbidity and disease progression.[47] While on treatment, patients with metastatic melanoma incur travel costs and costs associated with lost earnings from time off work.[48] 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.[42;49]

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®)[4] and dabrafenib (Tafinlar®),[5] and the MEK inhibitor trametinib (Mekinist),[9] 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.[8]

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.[50;51]

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%).[48] 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.[52] This serves to further emphasise the need for continued funding of research for this disease.

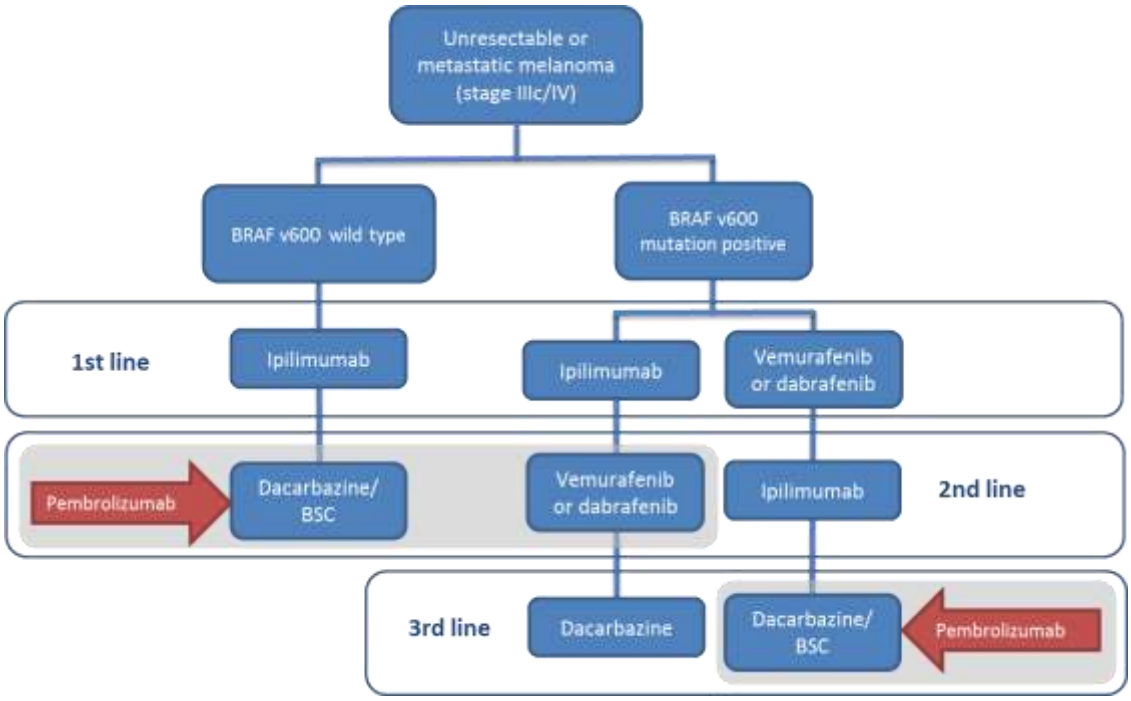
3.3: Clinical pathway of care showing the context of the proposed use of the technology

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 1st line treatment with a BRAF inhibitor, either vemurafenib (Zelboraf®; Roche)[15] or dabrafenib (Tafinlar®; GSK),[16] or with ipilimumab (Yervoy®; BMS). [1] A BRAF inhibitor is more likely to be used as the 1st 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.[53] 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).[54] For patients with negative BRAF^{V600} status (BRAF wild-type), ipilimumab is currently a recommended 1st line treatment option.[1] 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.[4-7]. The first approved IO agent, ipilimumab, has a marked benefit for a small proportion of patients,[8] although with a high immune-related AE profile.[14] Consequently there remains an unmet need, as most patients continue to face a remarkably poor prognosis.[4;5;55]

With this submission, pembrolizumab is proposed to be used as a 2nd or 3rd line treatment option for adult patients with unresectable or metastatic melanoma who have progressed following prior treatment with ipilimumab and, if BRAF^{V600} mutation positive, a BRAF or MEK inhibitor. The use of pembrolizumab is not precluded to patients who had received ipilimumab as the latest treatment prior to receiving pembrolizumab, but extends to any patients that have previously received ipilimumab, independently of the line of treatment (as shown in Figure 3 below). Therefore, pembrolizumab is expected to displace the use of BSC (including dacarbazine) to further subsequent lines of treatment for patients experiencing 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.[1;15;16;56] As a consequence, the use of pembrolizumab potentially reflects a step change in the management of patients with unresectable or metastatic melanoma. Clinicians in the UK have anticipated the positioning of pembrolizumab within the treatment pathway.[57]

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.[40] 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.[3]

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. Given current NICE treatment recommendations for unresectable or metastatic melanoma according to BRAF status, it is expected that 628 patients previously treated with ipilimumab (and if being BRAF^{V600} mutation-positive, a BRAF or MEK inhibitor) will be eligible for treatment with pembrolizumab in 2015. The projected number of patients eligible for treatment with pembrolizumab in the next 5 years is presented in Table 5.

Table 5: Estimated patient numbers for England, 2015-2019

Year	2015	2016	2017	2018	2019
Incidence of Malignant Melanoma	12,601	12,601	12,601	13,971	12,601
Eligible population Stage IIIc and IV	1,260	1,304	1,350	1,397	1,446
BRAF^{V600} Mutation-positive patients	252	212	195	196	203
BRAF^{V600} mutation-negative patients	376	114	105	109	113
Total stage IIIc and IV patients eligible for pembrolizumab in 2L or 3L	628	326	301	305	316

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).[1;15]

- 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.[2]

- 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.[16]

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.[58] 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.[59]

A NICE clinical guideline for the assessment and management of malignant melanoma is currently under consultation and is due for publication in July 2015.[56] 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:[1;2;15;16;56]

3.6: Details of other clinical guidelines and national policies

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

- European Society for Medical Oncology (ESMO). Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow up (2012) [60]
  - In these guidelines, ipilimumab was identified as an option for 1st and 2nd 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) [61]
  - 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.[62]

- 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 1st 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)[63]
  - These concise guidelines cross-refer to the treatment recommendations published by the British Association of Dermatologists (see above).
- 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.*"

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

We are not aware of any issues relating to current clinical practice. Comprehensive NICE guidance regarding treatment of metastatic melanoma is available (see section 3.5 and 3.6 above) and provides clear recommendations.

3.8: Equality issues

We do not anticipate 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 who have been previously treated with ipilimumab.

The following databases were searched from inception to 27 January 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 and the European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO) and Society of Melanoma Research (SMR) 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 and proceedings 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 6 below:

Table 6: Eligibility criteria used in the search strategy

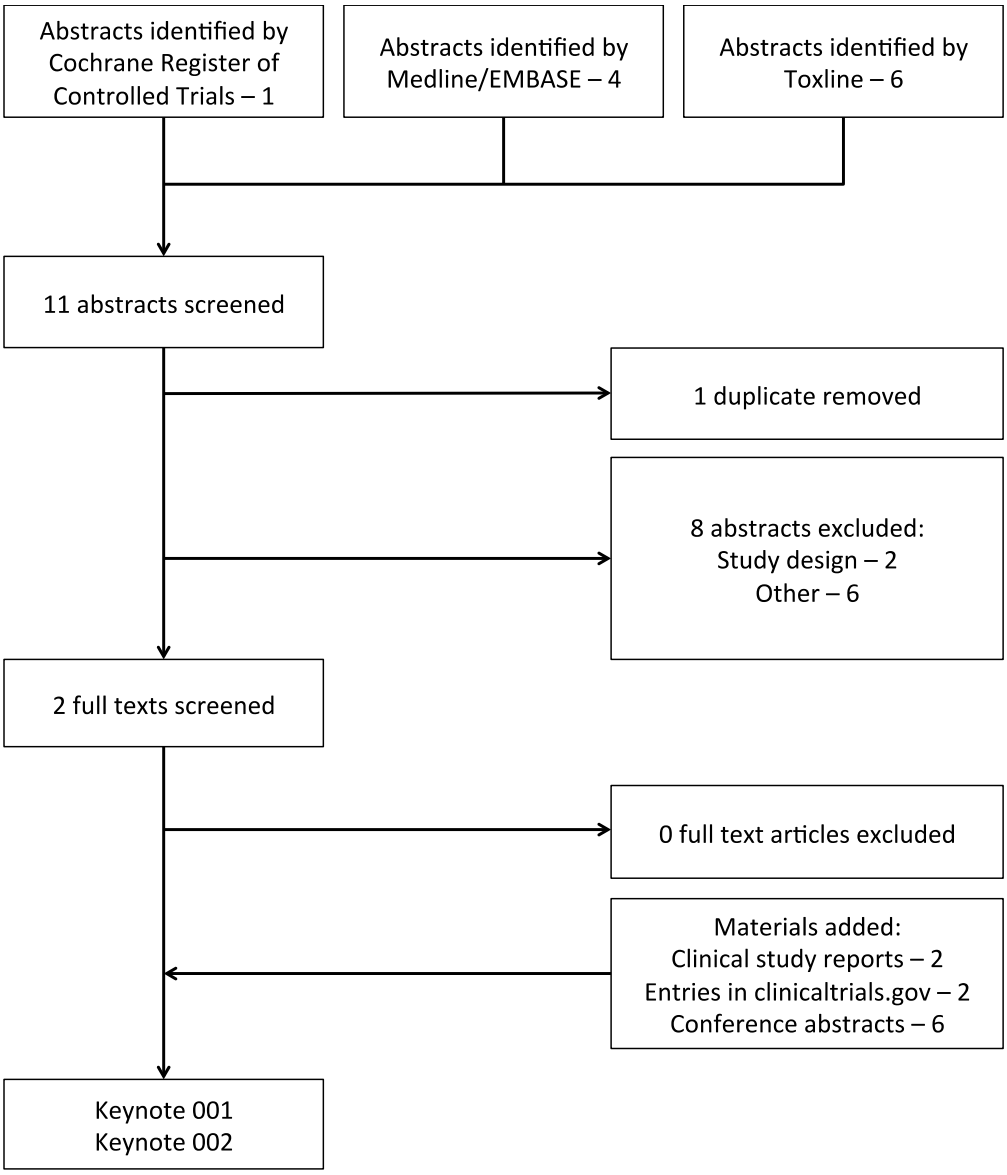
Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with unresectable stage III or IV melanoma previously treated with ipilimumab.	Patients with non-cutaneous melanoma (i.e. ocular or mucosal melanoma) and with unknown primary site
Intervention	Pembrolizumab / MK-3475	Any other intervention
Comparators	• Dacarbazine (DTIC) • Best supportive care*	Any other comparison
Outcomes	At least one of the following outcomes: • Overall response (OR) • Progression-free survival (PFS) • Overall survival (OS)	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	English	Any other language

**This intervention may be assessed in either ipilimumab-naïve or ipilimumab experienced populations.*

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

The electronic searches yielded 11 articles concerning pembrolizumab. Of these articles, 1 duplicate was removed and 8 were excluded during abstract screening, which led to 2 articles 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-001 data consists of one clinical study report,[65] three conference abstracts,[66-68] two peer-reviewed publications,[18;69] and one entry in clinicaltrials.gov;[70] KEYNOTE-002 data consists of one clinical study report[20], one conference abstract [68] and one entry in clinicaltrials.gov[71]

Execution of the search strategy and application of the inclusion/exclusion criteria resulted in 2 relevant RCTs (KEYNOTE-001[18;65-67;69;70;72] and KEYNOTE-002)[20;68;71] which evaluated the primary treatment of interest, pembrolizumab, in ipilimumab experienced populations.

4.1.5: Single study data drawn from multiple sources

KEYNOTE-002 data consists of one clinical study report, [71] one conference abstract [68] and one entry in clinicaltrials.gov.[20]

KEYNOTE-001 data consists of one clinical study report,[65] three conference abstracts,[66;67;72] two peer-reviewed publications,[18;69] and 1 entry in clinicaltrials.gov. The trial design of KEYNOTE-001 is presented in section 4.3.1. Only Part B2 of KEYNOTE-001 concerns a population of relevance to the decision problem. Data and results concerning Part B2 of KEYNOTE-001 are drawn from one clinical study report,[65] one peer-reviewed publication,[18] and 1 entry in clinicaltrials.gov[18]

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 7: List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
KEYNOTE-002	•Histologically or cytologically confirmed diagnosis of unresectable Stage III or metastatic melanoma not amenable to local therapy •Participants must be refractory to ipilimumab •Participants with BRAF gene mutant melanoma must have had a prior treatment regimen that included vemurafenib, dabrafenib, or an approved BRAF gene and/or MEK protein inhibitor	Pembrolizumab 2 mg/kg Q3W Pembrolizumab 10 mg/kg Q3W	Investigator choice chemotherapy (carboplatin + paclitaxel, carboplatin alone, paclitaxel alone, dacarbazine, or temozolomide)	• ClinicalTrials.gov reference: NCT01704287[71] • CLINICAL STUDY REPORT PN002[20] • Ribas et al. (2014) [68]
KEYNOTE-001 Part B2*	Histological or cytological diagnosis of melanoma. Melanoma must be measurable by imaging (*Part B2 represents "ipilimumab refractory" patients, and reflects the patient population included in KEYNOTE-002)	Pembrolizumab 2 mg/kg Q3W	Pembrolizumab 10 mg/kg Q3W	• ClinicalTrials.gov reference: NCT01295827[70] • CLINICAL STUDY REPORT P001V01[65] • Robert et al. (2014) [18]

Of the trials listed above, only KEYNOTE-002 compares the intervention with a comparator relevant to the decision problem. In KEYNOTE-002, the comparator of interest is investigator-choice chemotherapy (IV paclitaxel plus carboplatin, carboplatin alone, paclitaxel alone, dacarbazine, or oral temozolomide).

The currently available evidence base does not include a trial that evaluates pembrolizumab 2 mg/kg relative to BSC among ipilimumab experienced patients. Furthermore, there is no trial that compares chemotherapy with BSC in this population. However, an RCT comparing lenalidomide plus BSC and BSC alone as 2nd line treatment among patients not exposed to ipilimumab suggests that chemotherapy in addition to BSC, after failure of 1st line systemic treatment, demonstrates no benefit in terms of tumour response, time to progression, or overall survival.[13] Similarly, a non-randomised prospective study did not find that chemotherapy has any benefit over BSC in patients with advanced metastatic melanoma.[12] Extrapolation of this lack of efficacy among patients not previously treated with ipilimumab to patients previously treated with ipilimumab, suggest that the chemotherapy arm of KEYNOTE-002 can be considered a proxy for BSC regarding expected OS and PFS. This argument is further justified by the fact that dacarbazine is mostly used in a palliative setting outside of clinical trials[11] and there are no RCTs demonstrating an improvement in survival with dacarbazine relative to BSC / any other control agent.[11;12]

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-002: (Note: this study is ongoing, but no longer recruiting patients)

Trial design:

KEYNOTE-002 is a randomised, Phase II study of pembrolizumab versus chemotherapy in patients with advanced melanoma, refractory to ipilimumab.

Patients refractory to ipilimumab were defined as follows:

• Received at least two doses of ipilimumab (minimum dose of 3 mg/kg given every 3 weeks)

• Progressive disease (PD) after ipilimumab was defined according to Immune-related response criteria (irRC).[73] The initial evidence of PD was to be confirmed by a second assessment, no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression. Once PD was confirmed, initial date of PD documentation was considered the date of disease progression.

• Documented disease progression within 24 weeks of the last dose of ipilimumab. Patients who were re-treated with ipilimumab and patients who were on maintenance ipilimumab were allowed to enter the trial as long as there was documented PD within 24 weeks of the last treatment date with ipilimumab.

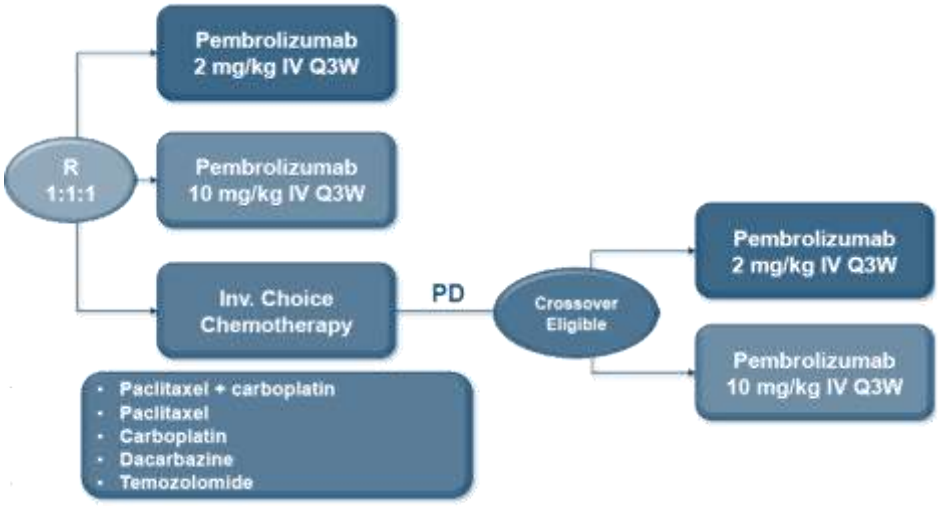
• Ipilimumab did not need to be the last treatment prior to entering the trial as long as the patient met the above described criteria.

Study medication for the pembrolizumab treatment arm was administered in a blind fashion on an outpatient basis as an IV infusion Q3W (± 2 days). Pembrolizumab 2 mg/kg or 10 mg/kg dosing was prepared by an unblinded pharmacist. Patients assigned to the chemotherapy arm received pre-treatment according to the Investigator's discretion based on standard of practice guidelines or current clinical practice.

Patients were allowed to continue on study therapy until disease progression, unacceptable toxicity, withdrawal of consent, physician's decision to stop therapy for the patient, or the study sponsor’s decision to terminate the study. All patients are being followed for survival outcome.

The design of KEYNOTE-002 is depicted in Figure 5 below:

Figure 5: Study design of KEYNOTE-002



Pembrolizumab dose assignments are blinded to investigators, patients and study sponsor.
PD = Progressive Disease
Crossover is permitted at Week 12 or beyond for PD confirmed by central review of imaging scan

Response criteria and patient management were evaluated by Response Evaluation Criteria In Solid Tumors (RECIST version 1.1).[74]

Radiologic tumor assessments were obtained as follows:

- Screening: Within 28 days prior to first dose of study medication
- Week 12: First radiologic assessment of tumour response following first dose of study medication. Scans obtained every 6 weeks until Week 48. Crossover permitted at Week 12 or beyond for PD. Must be confirmed by central review of imaging scan prior to crossover
- Week 48: After Week 48, scans obtained every 12 weeks.

If imaging at 12 weeks (or first tumour assessment) showed PD or tumour assessment indicated disease progression according to RECIST 1.1,[74] treatment with pembrolizumab may have continued until a repeat assessment 4-6 weeks later confirmed PD. If the repeat imaging showed evidence of disease stabilization or objective response (relative to the previous scan that showed PD) as per RECIST 1.1,[74] pembrolizumab may have been continued as per treatment calendar. If the repeat assessment showed disease progression relative to the previous scan that showed PD, then pembrolizumab was discontinued.

The decision to allow patients to continue treatment despite the initial radiologic progression took into account the observation that some patients with melanoma can have a transient tumour flare in the first few months after start of immunotherapy with subsequent disease response (see Appendix 1). A minimal set of criteria must have been met in order to continue pembrolizumab administration to patients with radiological PD at Week 12. Such criteria may have included the following:

- Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status[75]
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Eligibility criteria:

In order to be enrolled in KEYNOTE-002, patients must have received a diagnosis of metastatic melanoma, and have measureable disease (by CT scan or MRI) as defined by RECIST 1.1.[74]

Key inclusion criteria:

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

1) Histologically or cytologically confirmed diagnosis of unresectable Stage III or metastatic melanoma not amenable to local therapy
2) Participants must be refractory to ipilimumab (definition provided above under 'Trial design' at the start of section 4.3.1).
3) Participants with BRAF gene mutant melanoma must have had a prior treatment regimen that included vemurafenib, dabrafenib, or an approved BRAF gene and/or MEK protein inhibitor
4) Must consent to allow correlative studies; must provide a newly obtained tissue/biopsy specimen (or specimen obtained within 60 days of consenting)
5) Radiographically measurable disease
6) Eastern Cooperative Oncology Group (ECOG)[75] Performance Status of 0 or 1

Key exclusion criteria:

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

1) Chemotherapy, radiation therapy, or biological therapy within four weeks prior to the first dose of study drug, or not recovered from the adverse events (AEs) due to cancer therapies administered more than four weeks earlier
2) Disease progression within 24 weeks of last dose of ipilimumab
3) 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
4) Expected to require any other form of systemic or localized antineoplastic therapy while on study
5) Chronic systemic steroid therapy within two weeks before the planned date for first dose randomized treatment or on any other form of immunosuppressive medication
6) Known history of any other than the current malignancy excepting adequately treated basal or squamous cell carcinoma of the skin, superficial bladder cancer, in situ cervical cancer, breast cancer, or other in situ cancers
7) Known active central nervous system (CNS) metastases and/or carcinomatous meningitis
8) Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents
9) Prior treatment with any other anti-programmed cell death (PD) agent
10) Active infection requiring systemic therapy
11) Known history of Human Immunodeficiency Virus (HIV)
12) Active Hepatitis B or Hepatitis C
13) Regular user (including recreational use of) illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol)
14) 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:

This was a global study conducted in the following countries:

Argentina, Australia, France, Germany, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, United States.

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

Trial drugs and concomitant medications:

Patients were assigned to receive intravenous (IV) pembrolizumab 2 mg/kg (n = 180) or 10 mg/kg (n = 181) Q3W, or Investigator choice chemotherapies delivered according to standard of care (SOC) or current practice for the treatment of melanoma (choices were: IV paclitaxel plus carboplatin, carboplatin alone, paclitaxel alone, dacarbazine, or oral temozolomide; n =179)

Pembrolizumab was administered as a 30 minute IV infusion. An unblinded pharmacist was responsible for preparing the blinded pembrolizumab medication for administration.

Prior to randomisation, the Investigator was responsible for determining which chemotherapy would be administered in the event the patient was randomised to the chemotherapy arm of the study. Assigned chemotherapy was not permitted to be changed once the Cycle 1 Day 1 dose had been administered. Further details of the intervention and comparator regimens are provided in Appendix 4.

Primary, secondary and tertiary outcomes

Primary objectives:

The co-primary objectives were to evaluate the PFS and OS in patients with ipilimumab refractory advanced melanoma receiving either pembrolizumab or chemotherapy.

- PFS was defined as the time from randomisation to the first documented disease progression (based on assessment from a central imaging vendor using RECIST 1.1)[74] or death due to any cause, whichever occurred first.

- OS was defined as the time from randomisation to death due to any cause. Patients without documented death at the time of the final analysis were censored at the date of the last follow-up.

Secondary objectives:

The secondary objectives of the study included the assessment of the following

- overall response rate (ORR)
- response duration
- OS, PFS, and ORR in the biomarker positive subgroup defined by PD-L1 expression level (cut-off point to be estimated from external data) receiving either pembrolizumab or chemotherapy

- safety, tolerability and AE profile of single agent pembrolizumab 2 mg/kg and 10 mg/kg; the pharmacokinetics profile of single agent pembrolizumab at 2 mg/kg and 10 mg/kg.

ORR was defined as the proportion of the patients in the analysis population who had either a complete response (CR) or partial response (PR). Responses were based on confirmed assessments from a central imaging vendor using RECIST 1.1.[74]

Response Duration: For subjects who demonstrated confirmed CR or PR, response duration was defined as the time from first documented evidence of CR or PR until disease progression or death. The response duration for subjects who have not progressed or died at the time of analysis was censored at the date of their last tumour assessment.

Exploratory objectives:

The exploratory objectives were as follows:

- To evaluate ORR, PFS, OS, and DCR at Week 12.
- To evaluate health-related quality of life (HRQoL) changes from baseline using the EORTC-QLQC30.
- To characterize patient utilities using the EuroQoL EQ-5D.
- To evaluate the ORR, PFS, OS following crossover to pembrolizumab when treated with chemotherapy until disease progression.
- To investigate the relationship between candidate efficacy biomarkers and antitumor activity of pembrolizumab

PFS following crossover to pembrolizumab was defined as the time from first dose of crossover therapy to earliest documented disease progression (with respect to last available tumour assessments prior to crossover) or death due to any cause. OS following crossover to pembrolizumab was defined as the time from first dose of crossover therapy to death due to any cause.

Populations used for analysis:

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

KEYNOTE-001 - Part B2:

Trial design:

KEYNOTE-001, which formed the basis of the regulatory submission for pembrolizumab, 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 8 below:

Table 8: Part B and D of KEYNOTE-001

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: (data currently unavailable) Advanced melanoma patients:	125 patients at 10 mg/kg Q3W 123 patients at 10 mg/kg Q2W

Ipilimumab-naïve and ipilimumab-treated. Randomised to two dosing schedules	
D (population not relevant to decision problem) Advanced melanoma patients: Ipilimumab-naïve only. Randomized to two doses	51 patients at 2 mg/kg Q3W 52 patients at 10 mg/kg Q3W

Part B2 was a randomised expansion cohort of KEYNOTE-001, comprised of 173 patients who were refractory to ipilimumab and had received a BRAF (or MEK) inhibitor if they had BRAF mutant melanoma. In addition to evaluating the efficacy and safety of pembrolizumab in this population, Part B2 was also designed to further evaluate the dose of pembrolizumab by comparing 2 mg/kg or 10 mg/kg given every 3 weeks. This is the key patient population from KEYNOTE-001 supporting the use of pembrolizumab in a patient population comparable to that covered by the KEYNOTE-002 trial.

The 173 patients refractory to ipilimumab who were included in Part B2 were randomised to receive one of the following regimens:

- Pembrolizumab 2mg/kg Q3W (n=89)
- Pembrolizumab 10 mg/kg Q3W (n=84)

Melanoma patients from Part B2 (n=173 treated patients) of KEYNOTE-001 were part of an interim analysis. The data cut-off for safety and efficacy events included in this analysis was 18-Oct-2013.[65]

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 B2, treatment assignment was based on an 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 B: Part B patients had their first radiological disease assessment on study at Week 12 (± 1 week) unless clinical indication warranted earlier imaging.

If disease assessment at Week 12 showed stable disease (SD), 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.[73] Subsequent imaging was performed at Week 24.

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 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 B2 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 B2 of KEYNOTE-001 enrolled patients considered to be ipilimumab-refractory.
2) Measurable disease as defined per irRC.[73]
3) ECOG performance status[75] of 0 or 1.

Key exclusion criteria (Part B2 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.
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.
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, primary brain tumour or sarcoma, or of another 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 pneumonitis / interstitial lung disease.
10) Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents.
11) Received prior treatment targeting PD-1: PD-L1 axis or CTLA (with exception of ipilimumab), 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 173 patients were included in Part B2 of KEYNOTE-001. Patients were randomised to each of the following study arms:

- Pembrolizumab 2 mg/kg dose Q3W (n = 89)
- Pembrolizumab 10 mg/kg dose Q3W (n = 84)

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 B2 of KEYNOTE-001. The irRC[73] as assessed by investigators was applied as primary measure for assessment of tumour response. RR was also assessed based on RECIST 1.1[74] by blinded central reviewers as supportive analyses.

Secondary efficacy endpoint:

Disease Control Rate (DCR), response duration and PFS based on both irRC[73] and RECIST 1.1,[74] and OS served as secondary endpoints in this population.

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 9: Comparative summary of trial methodology

Trial number (acronym)	**KEYNOTE-002**	**KEYNOTE-001 (Part B2)**
Location	Global study conducted in multiple countries: Argentina, France, Germany, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, 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	Randomised, Phase II study of pembrolizumab versus chemotherapy in patients with advanced melanoma, refractory to 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 B2 represents the population of relevance to this submission
Key eligibility criteria for participants	• Histologically or cytologically confirmed diagnosis of unresectable stage III or metastatic melanoma not amenable to local therapy • Patients must be refractory to ipilimumab	**Part B2:** • Histological or cytological diagnosis of melanoma with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent

	• Patient with BRAF mutant melanoma must have had a prior treatment regimen that included vemurafenib, dabrafenib, or an approved BRAF and/or MEK inhibitor • ECOG performance status of 0 or 1	• Patients must be refractory to ipilimumab • Patients with BRAF^{V600} mutant melanoma must have had a prior treatment regimen that includes vemurafenib, dabrafenib, or other approved BRAF and/or MEK inhibitors • Patient must have progressive disease after the most recent treatment regimen
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 to receive one of the following regimens in KEYNOTE-002: • blinded pembrolizumab 2 mg/kg Q3W (n =180) • blinded pembrolizumab 10 mg/kg Q3W (n = 181) • investigator-choice chemotherapy (IV paclitaxel plus carboplatin, paclitaxel alone, dacarbazine, or oral temozolomide) according to standard of care (SOC) or current practice for the treatment of melanoma (n= 179) Disallowed concomitant medicines: • Any other investigational agent • Any other form of systemic or localized antineoplastic therapy • Chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study drug. • Chronic systemic steroid therapy within two weeks before the planned date for first dose randomised treatment or on any other form of immunosuppressive medication. • Treatment with live vaccines within 30 days prior to the first dose of study medication • Prior treatment with any other anti-PD-1, or PD-L1 or PD-L2 agent	Patients were randomised to each of the following study arms in Part B2 of KEYNOTE-001: • Pembrolizumab 2 mg/kg Q3W (n = 89) • Pembrolizumab 10 mg/kg Q3W (n = 84) Disallowed concomitant medicines: • 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
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	Primary efficacy endpoint: • RR to demonstrate the anti-tumour activity of pembrolizumab in the population enrolled under Part B2 of KEYNOTE-001. irRC as assessed by investigators was

	• OS: defined as the time from randomisation to death due to any cause PFS was based on assessment from a central imaging vendor using the 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. Crossover was permitted at Week 12 or beyond for PD. Must be confirmed by central review of imaging scan prior to crossover. After Week 48, scans were obtained every 12 weeks	applied as primary measure for assessment of tumour response. RR was also assessed based on RECIST 1.1 by blinded central reviewers as supportive analyses. 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 • Response duration • OS, PFS, and ORR in the biomarker positive subgroup defined by PD-L1 expression level • Further characterization of the PK profile of single agent pembrolizumab at 2 mg/kg and 10 mg/kg. • Safety, tolerability and adverse experience profile of single agent pembrolizumab 2 mg/kg and 10 mg/kg The exploratory objectives were as follows: • ORR, PFS, OS, and DCR at Week 12. • HRQoL changes from baseline using the EORTC-QLQC30. • Patient utilities using the EuroQoL EQ-5D. • ORR, PFS, OS following crossover to pembrolizumab when treated with chemotherapy until disease progression. • Relationship between candidate efficacy biomarkers and antitumor activity of pembrolizumab HRQoL questionnaires are	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

	performed up to Week 36 as well as at the End of Treatment, and 30-day Safety Follow-up visit	
Pre-planned subgroups	• PD-L1 biomarker subgroups (i.e. PD-L1 positive and PD-l1 negative subgroups) • Subgroup analyses of PFS were also performed based on clinically relevant baseline subject or tumour characteristics	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-002 [20]

Primary hypothesis

The study hypotheses were as follows:

- *Administration of pembrolizumab will result in a clinically meaningful improvement in PFS versus treatment with chemotherapy.*

- *Administration of pembrolizumab will result in a clinically meaningful improvement in OS versus treatment with chemotherapy*

Interim analysis and stopping guidelines

KEYNOTE-002 is currently ongoing although no longer recruiting patients. There were two planned interim analyses of KEYNOTE-002, as summarised in Table 10 below. Accrual was to be continued without a hold during the interim analyses.

Table 10: KEYNOTE-002: Summary of interim analysis strategy

Interim Analysis number	Key Endpoints for Interim Analysis	Anticipated approximate timing of Interim Analysis (from study start)	Sample size included for the analysis (three arms)	Purpose of analysis
Interim Analysis 1 (IA1)	ORR	10 months	120	Discontinue one inferior pembrolizumab arm
Interim Analysis 2 (IA2)	PFS/OS	15 months	510	• Demonstrate superiority of pembrolizumab in PFS • Stop for futility based on OS
Final Analysis	OS	24 months	510	Demonstrate superiority of pembrolizumab in OS

Sample size

540 patients were randomised with a 1:1:1 ratio into two pembrolizumab arms (2 mg/kg and 10 mg/kg) and one control arm (investigator choice chemotherapy). The study originally planned to randomise a total of 510 patients, but the protocol acknowledged that the study is OS event driven (i.e., number of patients and follow-up are subject to change but event number is not). If one of the pembrolizumab arms was discontinued at the interim analysis, the study was designed to complete after 245 deaths occurred in the remaining pembrolizumab arm and the control arm. The sample size calculation was based on the following assumptions:

1) OS follows an exponential distribution with a median of six months in the control arm
2) the hazard ratio (HR) between pembrolizumab and control is 0.65
3) an enrolment period of 15 months and a minimum of 9 months follow-up after enrolment completion; and
4) a drop-out rate of 2% in 12 months. If both pembrolizumab arms continued to the end, barring early stopping at interim analyses, the study was to be completed after 370 deaths have occurred (i.e., a 50% increase from 245)

The overall type I error rate for KEYNOTE-002 was strictly controlled at 2.5% (one-sided) with 0.5% allocated to PFS and 2% allocated to the OS hypothesis. Superiority of PFS was tested at the second interim analysis, and the Bonferroni method was used for multiplicity adjustment of the two pembrolizumab arms at this analysis, with each tested at 0.25%.

If any of the two pembrolizumab arms was demonstrated to have a superior PFS to the control arm, the corresponding alpha level was to be rolled into the OS hypothesis (i.e., the OS hypothesis will be tested at 2.0%, 2.25% and 2.5% respectively if none, exactly one or both hypotheses are rejected at the second interim analysis).

Because the alpha allocation for OS does not depend on event numbers, the overall type I error rate is well controlled when the actual event number at an interim analysis or at the final analysis differs from planned. For OS, 0.001% (negligible impact on overall type I error rate) was spent at the first interim analysis to prevent stopping the study prematurely and 0.5% was spent at the second interim analysis. Therefore, at the final analysis, OS will be analysed at 1.5%, 1.75% or 2% depending on the number of pembrolizumab arms demonstrating superior PFS to the control arm at the second interim analysis.
The Hochberg step-up procedure was used for OS testing at the second interim analysis and will be used at the final analysis, giving equal weight to the 2 mg/kg arm and 10 mg/kg arm, if neither is discontinued prior the analyses.

Statistical methods used to compare groups for primary and secondary outcomes

The statistical methods and analysis strategy for the primary and secondary efficacy endpoints are summarized in the Table 11 below:

Table 11: Analysis strategy for key efficacy endpoints

Endpoint (description , time point)	Approach*	Statistical method	Analysis population
Primary			
PFS	P	Stratified Log-rank test Cox model with Efrons's tie handling method for estimation was used to assess the treatment difference in PFS(i.e., hazard ratio and its 95% confidence interval) Kaplan-Meier (KM) method for PFS curve estimation in each treatment group	ITT
OS	P	Stratified Log-rank test Cox model with Efrons's tie handling method for estimation. KM method for OS curve estimation in each treatment group	ITT
Secondary			

ORR	P	Stratified M&N[$] method	FAS
Response Duration	P	Summary statistics using KM method	All responders

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

The same stratification factors used for randomisation were applied to both the stratified log-rank test and the stratified Cox model. Sensitivity analyses were performed for comparison of PFS based on investigator's assessment.

Since disease progression was assessed periodically, PD could occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD was documented. For the primary analysis, for the patients who had PD, the true date of disease progression was approximated by the date of first assessment at which PD was objectively documented per RECIST 1.1,[74] regardless of discontinuation of study drug.

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

To determine whether the treatment effect is consistent across various subgroups, 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)
- Baseline LDH level (normal vs. elevated LDH)
- BRAF mutation status
- Region (US, Ex-US)
- Chemotherapy (types with greater than 10% patients in the control group)
- PD-L1 expression (high vs. low) (depending on assay availability)
- Initial response to Ipilimumab (complete or partial response, stable disease for at least three months vs. progressive disease in three months)

The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above.

KEYNOTE-001 (Part B2) [65]

Primary hypothesis:

The study hypothesis was as follows:

Single agent pembrolizumab will show a clinically meaningful response rate in melanoma patients refractory to ipilimumab

Interim analysis and stopping guidelines

The study protocol specified that interim analyses of Part B ipilimumab refractory 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 B2 of KEYNOTE-001 randomised 89 patients to pembrolizumab 2 mg/kg Q3W and 84 patients to pembrolizumab 10 mg/kg Q3W.

The study protocol had originally planned to randomise 80 ipilimumab-refractory patients at each dose level, and stated the study had ~85% (or 96%) power to detect a 15% (or 20%) difference in RR between the two doses at the 10% type I error rate (one-sided) when the RR in the inferior arm is 10%. A p-value of 10% approximately corresponds to a 7% empirical difference in RR.

Statistical methods used to compare groups for primary and secondary outcomes

A 95% confidence interval for RR was provided for each population and by dose/schedule as applicable. Kaplan-Meier (KM) plots and descriptive statistics of PFS and OS were provided. Descriptive statistics were also provided for analysis of response duration and tumour volumetric change.

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 B2 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-002[20]

Trial population

The intention-to-treat (ITT) population served as the primary population for the analyses of PFS and OS in KEYNOTE-002. Patients were included in the treatment group to which they were randomised for the analysis of efficacy data using the ITT population.

The Full analysis set (FAS) population served as the primary population for the secondary endpoints of ORR. The FAS population consisted of all randomised patients with measurable disease at baseline based on independent central review that was blinded to treatment arms.

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

Missing data approach and censoring methods

The approach for dealing with missing data in the KEYNOTE-002 population is described in Table 12 below:

Table 12: KEYNOTE-002: Approach for dealing with missing data

Endpoint/Variable Response (Description, time-point)	Missing Data Approach
Primary:	
Progression-free survival	Model based
Overall survival	Model based

In order to evaluate the robustness of the PFS endpoint, two sensitivity analyses were performed with a different set of censoring rules. The first sensitivity analysis was the same as the primary analysis except that it censored at the last disease assessment without PD when PD or death was documented after more than one missed disease assessment. The second sensitivity analysis was the same as the primary analysis except that it considered discontinuation of treatment or initiation of new anticancer treatment, whichever occurred

later, to be a PD event for patients without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 13 below.

Table 13: Censoring rules for primary and sensitivity analyses of PFS

Situation	Primary analysis	Sensitivity analysis 1	Sensitivity analysis 2
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
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
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
PD or death documented after ≥ 2 missed disease assessment	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

A supportive analysis of OS that censored patients at crossover was performed.

For patients in the chemotherapy control arm, crossover to pembrolizumab was permitted following progression. Consequently adjustment of the OS was required to estimate OS in the chemotherapy arm in the absence of crossover. The RPSFT was pre-specified in the study protocol to adjust for the crossover effect without considering some of the relevant factors that determine the clinical validity of the approach, which should be assessed *a posteriori*. Following the NICE Decision Support Unit (DSU) recommendations for the adjustment of crossover in clinical trials,[76] additional crossover adjustments (two-stage and the IPCW) were implemented to estimate the actual chemotherapy-related OS in the absence of crossover (see sections 4.7 and 5.3.2).

KEYNOTE-001 (Part B2)[65]

Trial population

The primary efficacy analyses are based on the 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

Missing data approach and censoring methods

Not Applicable.

4.4.3: Statistical tests used in primary analysis

Table 14: Summary of statistical analyses in the RCTs

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
KEYNOTE-002	• Administration of pembrolizumab will result in a clinically meaningful improvement in PFS versus treatment with chemotherapy. • Administration of pembrolizumab will result in a clinically meaningful improvement in OS versus treatment with chemotherapy	The ITT population is the primary population for the analyses of PFS and OS. FAS population is the primary population for ORR. Patients were included in the treatment group to which they were randomised for the analysis of efficacy data using both the ITT and FAS populations.	OS event-driven study. Initially planned to randomise 510 patients with 1:1:1 ratio into two pembrolizumab arms and one control arm (540 patients were finally randomised). Sample size calculation was based on the following assumptions: 1) OS follows an exponential distribution with a median of 6 months in the control arm, 2) hazard ratio between pembrolizumab and control is 0.65, 3) an enrolment period of 15 months and a minimum of 9 months follow-up after enrolment completion, and 4) a dropout rate of 2% in 12 months. The overall type I error rate for this study is strictly controlled at 2.5% (one-sided) with 0.5% allocated to PFS at the second interim analysis and 2% allocated to OS.	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 B2)	• Single agent pembrolizumab will show a clinically meaningful response rate in melanoma patients refractory to ipilimumab	The primary efficacy analyses were based on the FAS population.	Part B2 initially planned to randomise 160 patients to pembrolizumab 2 mg/kg Q3W 10 mg/kg Q3W (89 patients were finally randomised to 2 mg/kg Q3W and 84 patients to 10 mg/kg Q3W). The study has ~85% (or 96%) power to detect a 15% (or 20%) difference in RR between the two doses at the 10% type I error rate (one-sided) when the RR in the inferior arm is 10%. A p-value of 10% approximately corresponds to a 7% 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.

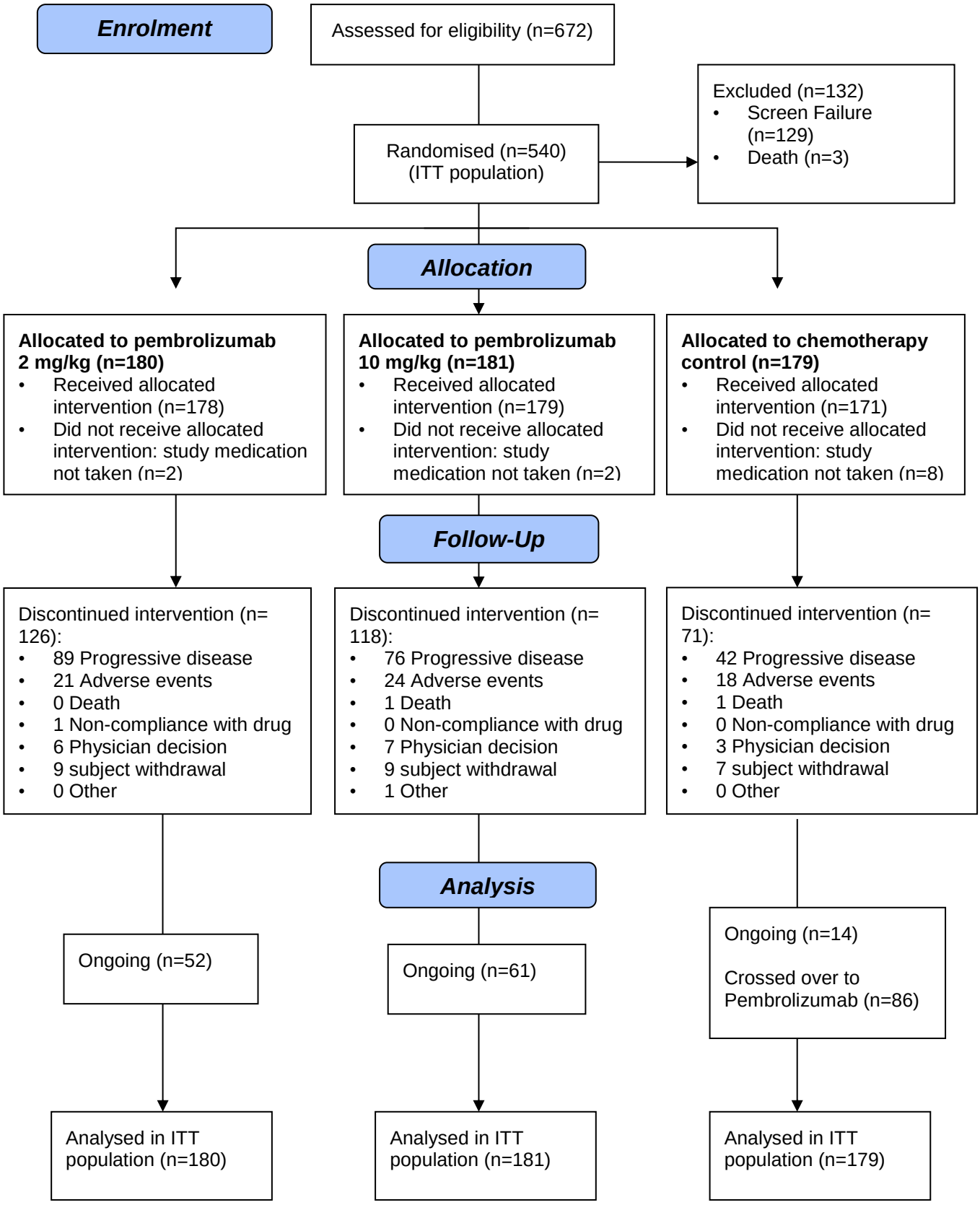
4.5 Participant flow in the relevant randomised controlled trials

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

KEYNOTE-002[20]

As KEYNOTE-002 is ongoing, the disposition of patients from randomisation through to last analysis cut-off (Interim-Analysis 2 [IA2]: May 2014) is presented in Figure 6 below:

Figure 6: CONSORT diagram – KEYNOTE-002



Patients assigned to Investigator-choice chemotherapy who experienced PD per RECIST 1.1[74] on chemotherapy (must have been confirmed by central review) and met all crossover criteria at Week 12 of study treatment, had the opportunity to crossover to pembrolizumab and receive 2 mg/kg or 10 mg/kg in a double-blind fashion.

The crossover criteria were as follows:

- Chemotherapy induced adverse events (except alopecia) must have improved to CTCAE (Version 4.0) ≤Grade 1
- If evidence of new or progression of previously treated brain metastases (inactive at the time of screening) requiring local therapy, the patient will not be eligible for cross over
- ECOG Performance Status 0-1
- Documentation of PD will be defined as per RECIST 1.1[74] (must be confirmed by central review)
- Consent to newly obtained tumour tissue biopsy that is obtained following last dose of chemotherapy and prior to receiving first dose of pembrolizumab study medication. Patients unable to provide a newly obtained tumor biopsy specimen will require sponsor approval.

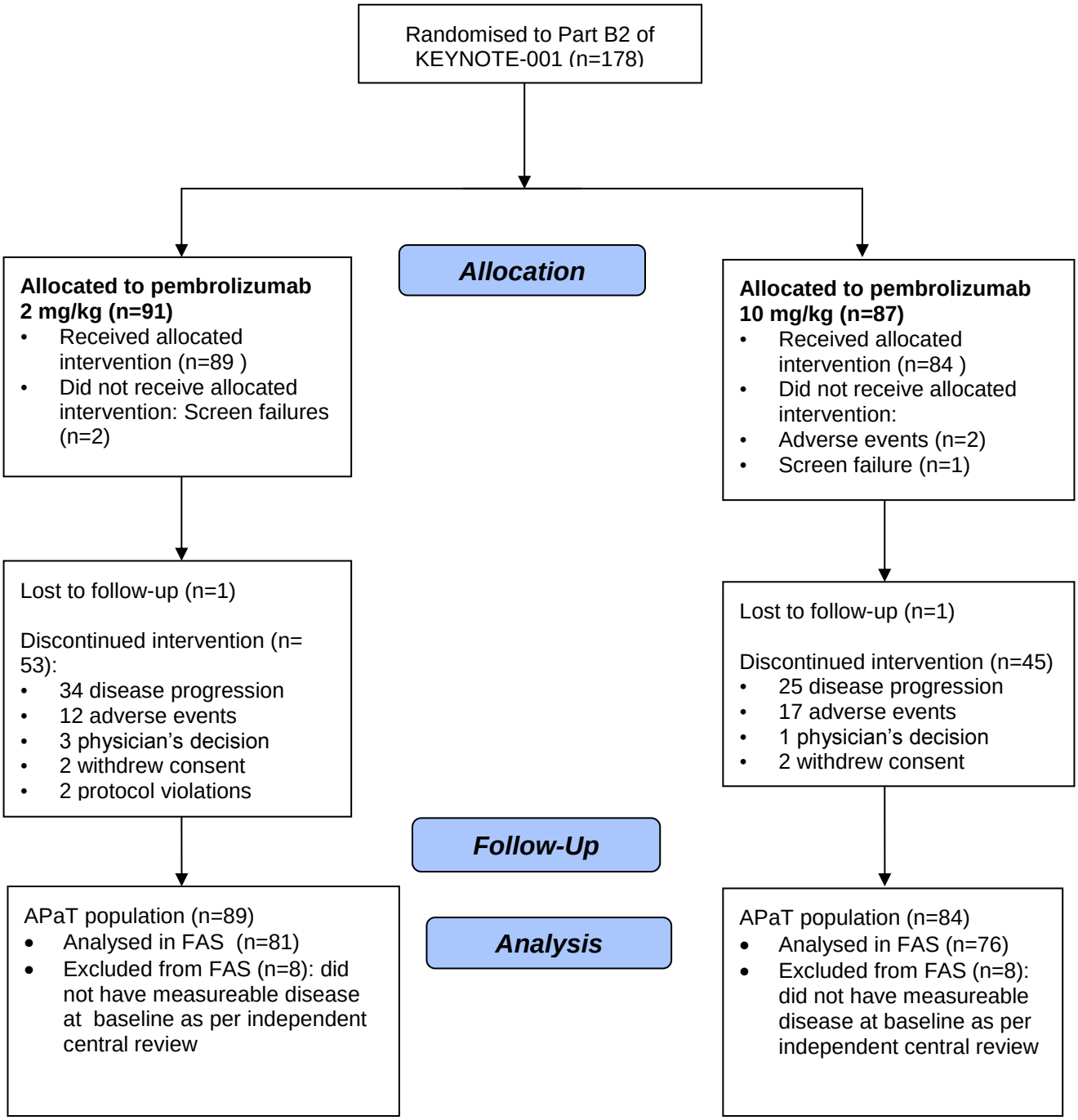
Patients who qualified, based on progressive disease criteria, must have completed a washout period for at least 28 days from last dose of chemotherapy before receiving randomised blinded dose of pembrolizumab 2 mg/kg or 10 mg/kg. After completing the washout period, the patient started the crossover phase.

Subjects/patients were allowed 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 subject/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.

KEYNOTE-001 Part B2[18;65]

The disposition of patients from randomisation through to database lock (October 2013) is presented in **Figure 7** below:

Figure 7: CONSORT diagram – KEYNOTE-001 Part B2



4.5.2: Characteristics of participants at baseline for each trial

KEYNOTE-002[65]

The 540 subjects enrolled represent a heavily pre-treated, advanced melanoma population who were refractory to ipilimumab (and previously treated with a BRAF inhibitor if indicated).

Subject characteristics at baseline were generally balanced between the three treatment arms of KEYNOTE-002, as shown in Table 15 below.

Table 15: Patient characteristics (ITT population)

	Pembrolizumab 2mg/kg Q3W n = 180	Pembrolizumab 10mg/kg Q3W n = 181	Chemotherapy n = 179	Total n = 540
Age, median (range), y	**62.0 (15-87)**	**60.0 (27-89)**	**63.0 (27-87)**	**61.5 (15-89)**
Male	58%	60%	64%	61%
ECOG PS[a]				
0	54%	54%	55%	55%
1	44%	46%	45%	45%
BRAF status				
Mutant	24%	22%	23%	23%
Wild Type	76%	78%	77%	77%
LDH Level[b]				
Normal	55%	58%	60%	58%
Elevated (≥110% ULN)	43%	40%	38%	40%
M stage				
M0	<1%	<1%	1%	<1%
M1a	5%	7%	8%	7%
M1b	12%	9%	8%	10%
M1c	82%	83%	82%	83%
No. of lines of previous therapies				
0	<1%[c]	0%	0%	<1%
1	22%	31%	26%	27%
2	44%	37%	44%	41%
≥3	33%	33%	30%	32%
Previous therapy[d]				
Ipilimumab	100%	100%	100%	100%
Interleukin-2	12%	9%	7%	9%
Other	14%	10%	13%	12%

immunotherapy[e]				
Chemotherapy	50%	46%	48%	48%
BRAF or MEK inhibitor[f]	26%	25%	24%	25%

[a]ECOG PS was missing for 2 patients.
[b]LDH level was unknown or missing for 11 patients. Analysis cut-off date: May 12, 2014.
[c]1 patient received ipilimumab in the adjuvant setting, which was not considered as a line of therapy.
[d]Patients may have received ≥1 type of previous therapy.
[e]Excludes ipilimumab and IL-2.
[f]Previous BRAF or MEK inhibitor treatment was a requirement for all patients with BRAF-mutant melanoma. Analysis cut-off date: May 12, 2014.

KEYNOTE-001 (Part B2)[18]

The 173 patients enrolled in Part B2 represent a heavily pre-treated, advanced melanoma population who were refractory to ipilimumab (and previously treated with a BRAF inhibitor if indicated). Patient characteristics, shown in Table 16 below, were generally balanced between 2 mg/kg Q3W and 10 mg/kg Q3W arms in this randomised cohort. There was a numerical difference in gender between the arms, with 68% male patients receiving treatment at 10 mg/kg Q3W and 54% male patients receiving treatment at 2 mg/kg Q3W. A higher number of $BRAF^{V600}$ mutant melanoma patients were assigned to the 10 mg/kg Q3W arm compared to the 2mg/kg Q3W arm (23% vs. 14%).

Prior oncologic therapies (excluding ipilimumab) between two dose arms were comparable while numerical difference was noted with respect to BRAF inhibitor exposure (which can be explained by a difference in number of BRAF mutant melanoma patients between arms). Of the patients who had BRAF mutant melanoma, all were treated with approved tyrosine kinase inhibitors (vemurafenib, dabrafenib, or trametinib) prior to study entry.

Table 16: Patients characteristics in Part B2 (APaT population):[18]

	Pembrolizumab 2mg/kg Q3W n = 89	**Pembrolizumab 10mg/kg Q3W n = 84**	**Total n = 173**
Age, (years, mean, range)	**57.0 (18.0-88.0)**	**60.7 (27.0-86.0)**	**58.8 (18.0-88.00)**
Male	54%	68%	61%
ECOG PS			
0	66%	68%	67%
1	34%	32%	33%
BRAF status			
Mutant	13%	23%	18%
Wild Type	87%	77%	82%

Brain metastasis			
Yes	8%	10%	9%
No	91%	89%	90%
Unknown	1%	1%	1%
LDH Level			
Normal	55%	66%	60%
Elevated	44%	35%	39%
Unknown	1%	0	<1%
Baseline tumour size*(mm; mean, range)	171 (15-895)	149 (14-535)	160 (14-895)
M stage			
M0	1%	1%	1%
M1a	11%	20%	16%
M1b	22%	17%	20%
M1c	65%	62%	64%
Previous systemic therapies			
1	33%	23%	28%
2	35%	40%	38%
≥3	33%	37%	35%
Previous therapy			
Ipilimumab	100%	100%	100%
Immunotherapy, excluding ipilimumab	30%	31%	31%
Chemotherapy	44%	49%	46%
BRAF or MEK inhibitor, or both[f]	16%	24%	20%

**Baseline tumour size was calculated as the sum of the longest diameters of all target lesions for patients with measurable disease by RECIST 1.1 criteria (version 1.1) by independent central review at baseline*

.[f]The number of patients with previous treatment with a BRAF or MEK inhibitor, or both, is greater than the number of patients with BRAF-mutant melanoma because those with a BRAF wild-type melanoma could have received a MEK inhibitor in a clinical trial.

4.6 Quality assessment of the relevant randomised controlled trials

A complete quality assessment for each RCT is included in Appendix 5.

A tabulated a summary of the quality assessment results is presented in Table 17 below.

Table 17: Quality assessment results for parallel group RCTs

Trial	KEYNOTE-002	KEYNOTE-001 (Part B2)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No
Were there any unexpected imbalances in drop-outs between groups?	No	Not clear
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-002 Results[20;68]: Interim analysis 2 (IA2) - data cut-off 12 May 2014

Clinical effectiveness results are presented in this section for pembrolizumab 2 mg/kg Q3W (anticipated licence dose; and dosage relevant to this submission) versus the comparator of interest (investigator choice chemotherapy). Full results for all three study arms (including pembrolizumab 10 mg/kg Q3W) are presented as an appendix (See Appendix 6).

Summary:

PFS and OS are the co-primary endpoints in this trial. The primary endpoint for IA2 was PFS.

The study commenced in October 2012, and completed enrolment in November, 2013, ahead of the predicted date of February, 2014. Due to the faster enrolment and lower death rate than expected, the actual timing of IA2 was driven by the targeted 210 deaths. The data cut-off date for IA2 was set to May 12, 2014 based on the trigger event of 210 deaths. The actual number

of deaths was 215 and the actual number of PFS events was 410 (based on central assessment of disease status) in this analysis.

The study allowed crossover which confounded OS analysis results. Subjects in the control arm were allowed to cross over to pembrolizumab arm (dose level pre-decided at original randomisation) after Week 12 and once the progressive disease was confirmed by the IRO (central review). By the time of the data cut-off for IA2 (i.e., 12 May 2014), a total of 86 of 179 subjects (48%) who were randomised to the control arm had crossed over and were treated with pembrolizumab.

An overview of the study population is provided in Table 18 below:

Table 18: KEYNOTE-002 study population

	Control Group N	Pembrolizumab 2 mg/kg Q3W n	Pembrolizumab 10 mg/kg Q3W n	Total n
Number of patients screened				672
Number of patients randomised (ITT population)	179	180	181	540
Number of patients received treatment (APaT population)	171	178	179	528
Crossed over to pembrolizumab	86			
Number of patients with measurable disease at baseline per IRC (FAS population per IRC)	165	165	163	493
Number of patients with measurable disease at baseline per Investigator (FAS population per Investigator)	179	180	181	540

IRC = Independent Review Committee

A summary of the clinical efficacy outcome results based on IA2 for pembrolizumab 2 mg/kg Q3W versus chemotherapy are presented in Table 19 below:

Table 19: KENOTE-002 - Overall summary of efficacy

	2 mg/kg Q3W	Control
Number of Subjects	180	179
PFS (IRO [central review] per RECIST 1.1)		
HR - Treatment vs Control (95% CI)	0.57 (0.45, 0.73)	--
Median in months (95% CI)	2.9 (2.8, 3.8)	2.7 (2.5, 2.8)

	2 mg/kg Q3W	Control
P value†	<0.0001	
6 month PFS rate (%)	34.3 (27.4, 41.3)	15.6 (10.5, 21.5)
OS		
Median in months • Unadjusted for crossover • Control: RPSFT correction • Control (Two-stage correction - simple model • Control (Two-stage correction – all covariates) • Control (IPCW)	11.4 (10.2, NR)	11.6 (9.0, 16.3) 11.1 (9.7, NR) 7.8 (5.3, 9.7) 7.9 (5.4, 9.7) 7.5*
OS rate at Month 3 (%) (95% CI)	85.5 (79.4, 89.9)	85.3 (79.2, 89.8)
HR: pembrolizumab 2mg/kg vs control (95% CI); p-value • Unadjusted for crossover • Control: RPSFT correction • Control (Two-stage correction - simple model • Control (Two-stage correction – all covariates) • Control (IPCW correction)	0.88 (0.64, 1.22); p = 0.229 0.81 (0.50, 1.23), p = 0.229 0.63 (0.45, 0.88) p = 0.006 0.63 (0.45, 0.88) p= 0.007 0.68 (0.48, 0.96) p = 0.028	--
ORR analysis (IRO [central review] per RECIST 1.1)		
ORR – ITT (%) (95% CI)	21.1 (15.4,27.8)	4.5 (1.9,8.6)
Difference in % vs. Control (95% CI) (p value) ‡	12.8 (7.0,20.6) (p<0.0001)	--
Response duration1 (IRO [central review] per RECIST 1.1)		
Subjects with a responses (n)	38	8
Median in weeks (range)	Not reached (6+ - 50+)	37 (7+ - 41)
Non-progressing (non-PD) subjects n (%)	35 (92)	5 (63)
Median time to response in weeks (range)	13 (12-30)	13 (12-18)

NR: Not reached.
†Based on the stratified log-rank test.
‡ Based on stratified on Miettinen & Nurminen method.
** The IPCW approach does not produce median (and its confidence interval) as one of the model outputs. In order to find the time point when 50% of the patients on the Control were still alive, the estimated hazard ratio from IPCW (0.677) was applied to the Kaplan-Meier curve of pembrolizumab 2 mg/kg for an estimated OS curve for the Control group. For the adjusted OS curve of the Control group, it showed that the median OS*

	2 mg/kg Q3W	Control
is between 32 and 33 weeks		

Efficacy results are presented in more detail below:

Primary Endpoints

PFS: IA2 - Data cut-off 12 May 2014

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

Treatment with pembrolizumab is associated with a substantial improvement in PFS compared to chemotherapy. The improvement is statistically significant and clinically meaningful in subjects with ipilimumab-refractory melanoma. Table 20 and Figure 8 summarize the PFS based on central review. The hazard ratio (HR) for pembrolizumab 2 mg/kg Q3W versus the control arm is 0.57 (95% CI; 0.45, 0.73) [p <0.0001] favouring the pembrolizumab arm. The median PFS is 2.9 months in the pembrolizumab 2 mg/kg Q3W arm and 2.7 months in the control arm, occurring at approximately the time of the first scheduled response assessment (Week 12).From week 12 onwards the PFS rates begin to show separation, and dramatically separate thereafter (Figure 8), reflected by a 6 month PFS rate of 34.3% (95% CI; 27.4%, 41.3%) in the pembrolizumab 2 mg/kg arm, compared to 15.6% (95% CI; 10.5%, 21.5%) in the control arm, and a 9-month PFS rate of 23.7% (95% CI; 17.0, 31.1) in the pembrolizumab 2 mg/kg arm compared to 8.0% in the chemotherapy control arm (95% CI; 4.0, 13.9) (Table 21).

The PFS results using sensitivity censoring rule 1 (Table 13) are identical to the primary PFS analysis using primary censoring rules. Additionally, the PFS results using the censoring rule 2 (Table 13) are consistent with the primary PFS analysis.

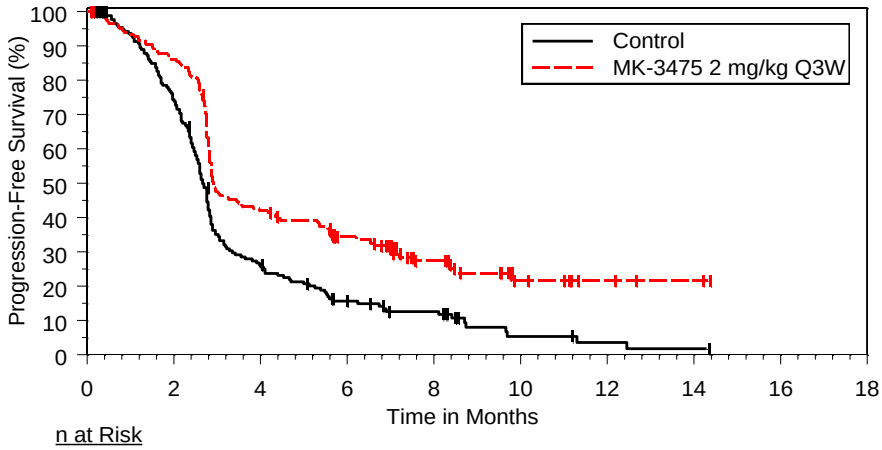
Table 20: KEYNOTE-002 - analysis of PFS based on central (IRO) assessment - primary censoring rule - (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS rate at 6 Months in %† (95% CI)	Treatment vs. control	
							Hazard Ratio‡ (95% CI)‡	p-value§
Control	179	155 (86.6)	584.3	26.5	2.7 (2.5, 2.8)	15.6 (10.5, 21.5)		

Pembrolizumab 2 mg/kg Q3W	180	129 (71.1)	804.6	16.0	2.9 (2.8, 3.8)	34.3 (27.4, 41.3)	0.57 (0.45, 0.73)	<0.0001

† From product-limit (KM) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ One-sided p-value based on stratified log-rank test.

Figure 8: KEYNOTE-002 - KM of PFS based on central (IRO) assessment (primary censoring rule) – ITT population



n at Risk										
Control	179	128	43	22	15	4	2	1	0	0
MK-3475 2 mg/kg Q3W	180	153	74	53	26	9	4	2	0	0

Table 21: KEYNOTE-002 - PFS rate at fixed time-points based on central (IRO) assessment per RECIST 1.1 (ITT population)

Treatment	PFS Rate at Month 3 in %† (95% CI)	PFS Rate at Month 6 in %† (95% CI)	PFS Rate at Month 9 in %† (95% CI)	PFS Rate at Month 12 in %† (95% CI)
Control	35.0 (27.9, 42.2)	15.6 (10.5, 21.5)	8.0 (4.0, 13.9)	3.6 (0.9, 9.5)
Pembrolizumab 2 mg/kg Q3W	47.5 (40.0, 54.7)	34.3 (27.4, 41.3)	23.7 (17.0, 31.1)	21.6 (14.5, 29.6)

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

- *PFS analyses based on INV evaluation using RECIST 1.1*

PFS analysis by INV assessments supported the marked improvement in PFS as observed by central review. Table 22 and Figure 9 summarize the PFS based on INV assessment. The HR for pembrolizumab 2 mg/kg Q3W arm versus the control arm was 0.49 (95% CI; 0.38, 0.62) favouring the pembrolizumab arm (p <0.0001), which is consistent with the PFS results based

on central review. The median PFS was 3.7 months in the 2 mg/kg Q3W pembrolizumab arm and 2.6 months in the control arm.

Table 23 summarizes the PFS rates at Month 3, 6, 9, and 12, which quantitatively illustrates the magnitude of benefit of pembrolizumab relative to chemotherapy. The PFS curves (Figure 9) begin to show separation, and a substantial difference is noted, by the first assessment time point with a 3-month PFS rate of 54.7% (95% CI, 47.1, 61.7) in the pembrolizumab 2 mg/kg arm compared to 32.9% (95% CI. 25.9%, 39.9%) in the control arm. The curves continue to separate thereafter, reflected by a 6 month PFS rate of 38.9% (95% CI; 31.6, 46.1) in the pembrolizumab 2 mg/kg arm compared to 15.2% (95% CI; 10.2, 21.0) in the control arm. The gap of PFS rate between pembrolizumab and control arms continued to expand toward the tail end of the PFS curves.

Table 22: KEYNOTE-002 - Analysis of PFS based on INV 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 6 Months in %† (95% CI)	Treatment vs. control	
							Hazard Ratio‡ (95% CI)‡	p-value§
Control	179	157 (87.7)	594.1	26 .4	2.6 (2.4, 2.8)	15.2 (10.2, 21.0)		
Pembrolizumab 2 mg/kg Q3W	180	122 (67.8)	864.7	14.1	3.7 (2.9, 5.4)	38.9 (31.6, 46.1)	0.49 (0.38, 0.62)	<0.0001

† From product-limit (KM) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ One-sided p-value based on stratified log-rank test.

Figure 9: KEYNOTE-002 - KM of PFS based on INV assessment (primary censoring rule) – ITT population

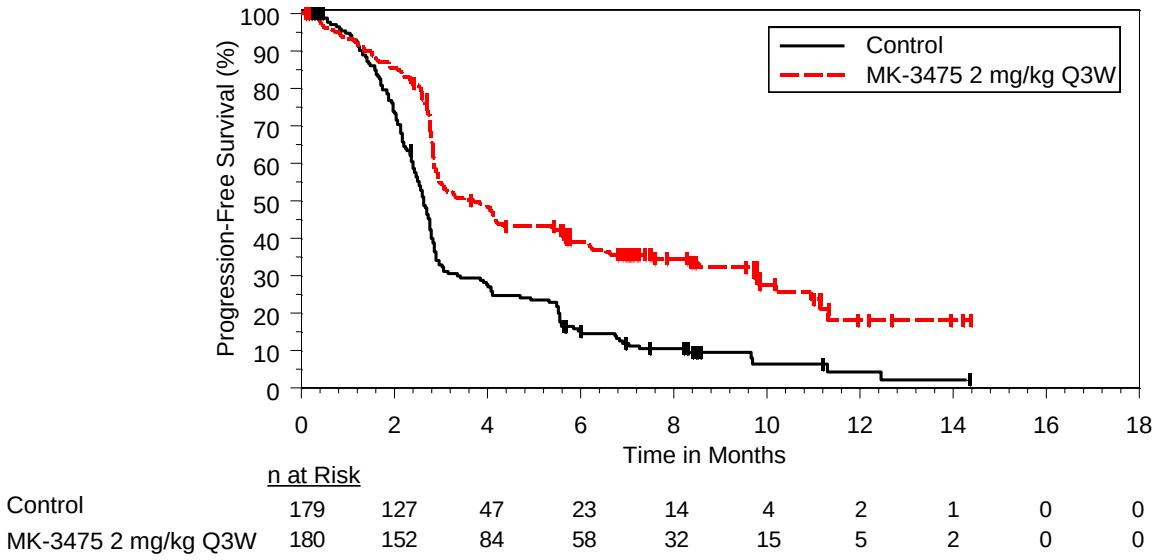


Table 23: KEYNOTE-002 - PFS rate at fixed time-points based on INV assessment per RECIST 1.1 (ITT population)

Treatment	PFS Rate at Month 3 in %† (95% CI)	PFS Rate at Month 6 in %† (95% CI)	PFS Rate at Month 9 in %† (95% CI)	PFS Rate at Month 12 in %† (95% CI)
Control	32.9 (25.9, 39.9)	15.2 (10.2, 21.0)	9.5 (5.5, 14.8)	4.2 (1.1, 10.7)
Pembrolizumab 2 mg/kg Q3W	54.7 (47.1, 61.7)	38.9 (31.6, 46.1)	32.2 (24.8, 39.7)	18.0 (9.7, 28.3)

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

OS: IA2 - Data cut-off 12 May 2014

Treatment with pembrolizumab showed a numerical trend toward improved OS when compared to the control arm. The improvement was not statistically significant at the time of IA2, primarily due to crossover permitted in the study (from chemotherapy to a pembrolizumab arm, following progression on chemotherapy). Table 24 summarizes the OS data. The HR for OS was 0.88 in the pembrolizumab 2 mg/kg Q3W arm over the control arm (p=0.229). The median OS was 11.4 months in the pembrolizumab 2 mg/kg Q3W arm and 11.6 months in the control arm (Table 24 and Figure 10).

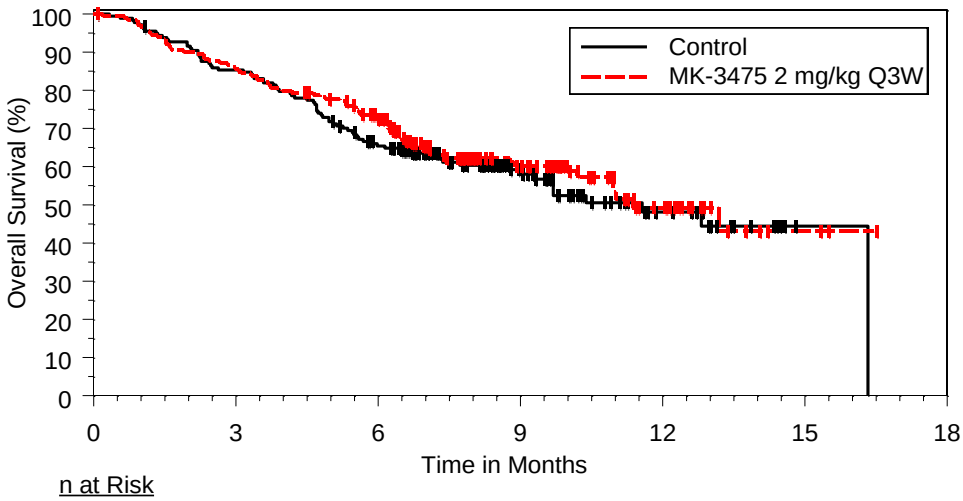
Due to extensive censoring and a small number of subjects at risk beyond 6 months, the median OS should be interpreted cautiously. The pre-specified final OS analysis will be performed after 370 deaths have occurred.

Table 24: KEYNOTE-002 - Analysis of OS - (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS rate at Month 3 in %† (95% CI)	Treatment vs. control	
							Hazard Ratio‡ (95% CI)‡	p-value§
Control	179	78 (43.6)	1247. 2	6.3	11.6 (9.0, 16.3)	85.3 (79.2, 89.8)		
Pembrolizumab 2 mg/kg Q3W	180	73 (40.6)	1289.6	5.7	11.4 (10.2, .)	85.5 (79.4, 89.9)	0.88 (0.64, 1.22)	0.2294

† From product-limit (KM) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ One-sided p-value based on stratified log-rank test.

Figure 10: KEYNOTE-002 - KM of OS



n at Risk							
Control	179	151	110	49	17	1	0
MK-3475 2 mg/kg Q3W	180	153	119	56	18	3	0

Modelling Approaches on OS Analysis Adjusted for Crossover Effect

The crossover rate of subjects randomised and treated with chemotherapy was 48%. In order to adjust for the crossover effect in the OS analysis, a pre-specified analysis utilizing the RPSFT method was conducted. The adjusted hazard ratio was 0.81 (95% CI; 0.51, 1.16) for

the pembrolizumab 2 mg/kg Q3W arm over the control arm (Table 25 and Figure 11). The RPSFT analysis of OS data is largely consistent with data from the primary analysis at IA2 except as expected; the treatment effect is slightly greater after adjusting for the crossover effect.

The RPSFT method had been pre-specified in the study protocol to adjust for the anticipated crossover effect in advance of the availability of trial based information needed to determine the clinical validity of the approach, which should be assessed *a posteriori*. Following the NICE DSU recommendations for the adjustment of crossover in clinical trials,[76] additional crossover adjustments (two-stage and the IPCW) were implemented to better understand the chemotherapy-related OS in the absence of crossover. Based on the trial characteristics, the switching mechanism, the proportion of patients switching and the clinical validity of the outputs obtained,[76] the two-stage adjustment was found to be the most appropriate method for this adjustment (see section 5.3.2).

For the two-stage crossover analysis, two models were run, one which adjusted for all relevant covariates (including: ECOG, tumour size, LDH, BRAF status, melanoma stage and age; (Figure 12) and a second, simple model which only incorporated ECOG (Figure 13). Both models demonstrated a separation between the pembrolizumab and the adjusted control arm. As presented in Table 25, after the two-stage adjustment pembrolizumab was shown to result in a significant improvement in OS compared to the adjusted control arm, independently of the model used (complete vs. simple), since both models led to similar results. Additionally, the median OS obtained from the two-stage adjustment was approximately 7.9 months in the chemotherapy control arm (Table 26), which was in line with what would be expected from metastatic melanoma patients treated with chemotherapy based on available evidence.[77-79] The two-stage adjusted results (HR of pembrolizumab vs. chemotherapy = 0.6324; 95% CI: 0.4525, 0.8843) were consistent with those obtained by the IPCW adjustment (HR = 0.677; 95% CI: 0.478, 0.959) (see section 5.3.2 for further detail).

Table 25: KEYNOTE-002 – Analysis of treatment versus control - crossover analysis

Crossover correction method	Pembrolizumab 2mg/kg vs. control	
	Hazard Ratio (95% CI)	p-value
Control (RPSFT correction)	0.81 (0.50, 1.23)	0.229
Control (Two-stage correction - Simple model)	0.63 (0.45, 0.88)	0.006

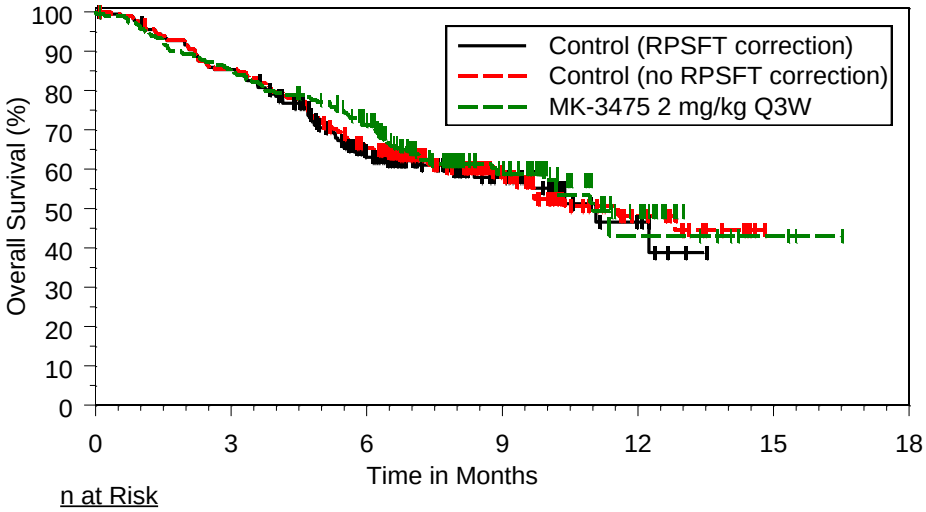
Control (Two-stage correction – All covariates)	0.63 (0.45, 0.88)	0.007
Control (IPCW correction)	0.68; (0.478, 0.959)	0.028

Table 26: KEYNOTE-002 - Analysis of Median OS using RPSFT, Two-stage and IPCW methods

Treatment	**Median OS (Months) (95% CI)**
Control (no crossover correction)	11.6 (9.0, 16.3)
Control (RPSFT correction)	11.1 (9.7, NR)
Control (Two-stage correction - Simple model)	7.8 (5.3, 9.7)
Control (Two-stage correction – All covariates)	7.9 (5.4, 9.7)
IPCW	7.5*
Pembrolizumab 2 mg/kg Q3W	11.4 (10.2, NR)

NR = not reported
**The IPCW approach does not produce median (and its confidence interval) as one of the model outputs. In order to find the time point when 50% of the patients on the Control were still alive, the estimated hazard ratio from IPCW (0.677) was applied to the Kaplan-Meier curve of pembrolizumab 2 mg/kg for an estimated OS curve for the Control group. For the adjusted OS curve of the Control group, it showed that the median OS is between 32 and 33 weeks*

Figure 11: KEYNOTE-002 - KM of OS using RPSFT (ITT population)



n at Risk							
Control (RPSFT correction)	179	151	84	29	8	1	0
Control (no RPSFT correction)	179	151	110	49	17	1	0
MK-3475 2 mg/kg Q3W	180	153	119	56	18	3	0

Figure 12: KEYNOTE-002 - Two- stage crossover analysis- All covariates

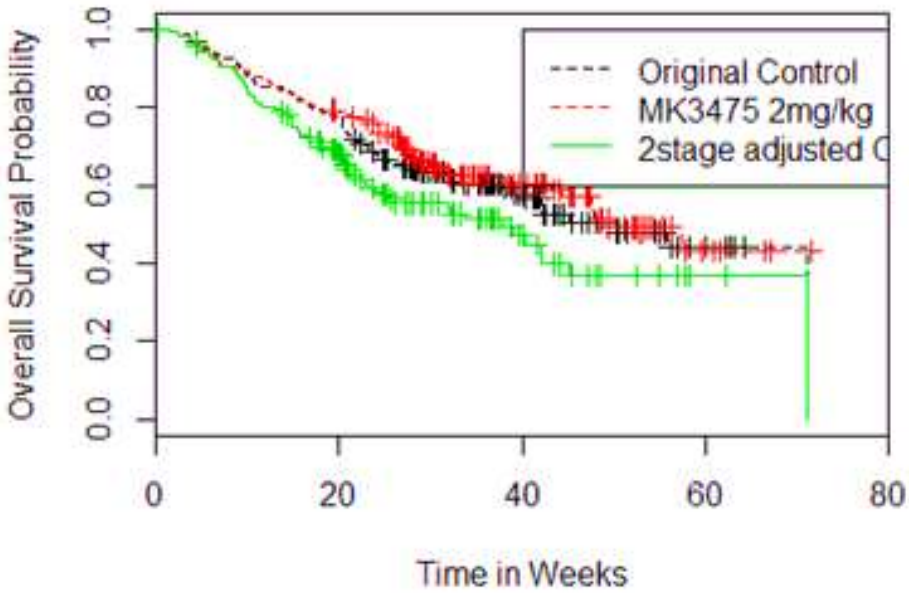
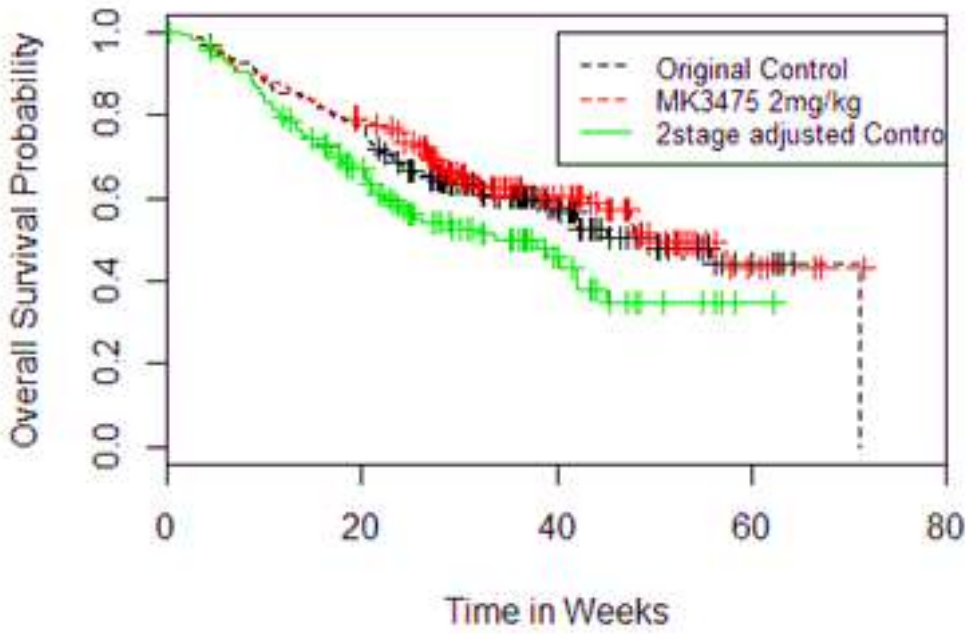


Figure 13: KEYNOTE-002 - Two-stage crossover analysis - Simple model



Secondary endpoints

ORR: IA2 - Data cut-off 12 May 2014

- *ORR– ITT population:*

Overall response rate is a key secondary endpoint of KEYNOTE-002. The primary method of analysis is based on independent central review (IRO assessment) of response using RECIST 1.1 and results are summarised in Table 27.

Pembrolizumab demonstrated a markedly higher confirmed objective response rate compared to chemotherapy in the control arm. Improvement of ORR with pembrolizumab is 4 to 5 fold, and the difference is highly statistically significant: ORR was 21% in the pembrolizumab 2 mg/kg arm and 4% in the chemotherapy arm (p<0.0001 for pembrolizumab versus chemotherapy). The difference of response rate between the pembrolizumab and the control arms is estimated using the stratified Miettinen & Nurminen method. The confirmed response rate difference is 12.8% for pembrolizumab 2 mg/kg Q3W vs. control (p<0.0001 for the pembrolizumab arm).

Table 27: KEYNOTE-002 - Analysis of OR based on central (IRO) assessment - ITT population

Treatment	N	Number of Overall Responses	Overall Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI) †	p-value ††
Control	179	8	4.5 (1.9,8.6)		
Pembrolizumab 2 mg/kg Q3W	180	38	21.1 (15.4,27.8)	12.8 (7.0,20.6)	<0.0001

Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1) and LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Table 28 summarises best overall response results by central review (IRO assessment) using RECIST 1.1. No CR was observed in the control group compared with 4 in the pembrolizumab 2 mg/kg Q3W arm. The disease control rate (CR+PR+SD) is 38.9% (70 subjects) in pembrolizumab 2 mg/kg Q3W arm, and 22.9% (41 subjects) in control arm.

Table 28: KEYNOTE-002 - Summary of best response based on central (IRO) assessment – ITT population

	Control Group		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Number of Subjects in Population				
Number (%) of Subjects with Best Response:				
• **Complete Response (CR)**	0	0.0	4	2.2
• **Partial Response (PR)**	8	4.5	34	18.9
• **Stable Disease (SD)**	33	18.4	32	17.8
• **Progressive Disease (PD)**	111	62.0	84	46.7
• **Not Evaluable**	27	15.1	24	13.3
• **No Disease**	0	0.0	1	0.6
• **No Assessment**	0	0.0	1	0.6

- *ORR: INV assessment – ITT population:*

  Similar to the ORR analysis based on central assessment (IRO), pembrolizumab showed clear superiority to chemotherapy in ORR analysis based on INV assessment per RECIST 1.1. The ORR is 21.1% in the pembrolizumab 2 mg/kg Q3W arm and 5.0% in the control arm (p <0.0001 for the pembrolizumab arm). There were no subjects with complete response in the control arm compared with 2.8% (n=5) of subjects with confirmed complete responses in the pembrolizumab dose arm.

- *ORR - FAS population*

  Response rates are generally similar between the ITT and FAS populations, but are slightly lower in the ITT population than the FAS population when using IRO assessment due to the inclusion of subjects who cannot achieve PR by RECIST 1.1 definition.

Response duration – central (IRO) assessment: IA2 - Data cut-off 12 May 2014

Table 29 provides a summary of the time to first confirmed objective response and the response duration for the treatment arms by central review (IRO) based on RECIST 1.1. At the time of analysis, approximately 92% of subjects in the pembrolizumab 2 mg/kg arm had not progressed vs. 63% in the control arm. There were 8 objective responders in the control arm as opposed to 38 responders in pembrolizumab 2 mg/kg Q3W arm. The median time to response was 13 weeks in both the pembrolizumab 2 mg/kg Q3W arm and in the control arm, largely consistent with the time of first post-baseline tumour assessment.

Median duration of response was not yet reached in the pembrolizumab 2 mg/kg arm and was 37 weeks in the chemotherapy arm. Due to the small number of subjects at risk at the median, the median response duration for the control arm should be interpreted cautiously. However, a substantial difference in the proportion of subjects without an event of disease progression is noted. Figure 14 provides the KM curves demonstrating the overall duration of response based on central review (IRO assessment). A total of 87% of subjects in the pembrolizumab 2 mg/kg arm had response ongoing.

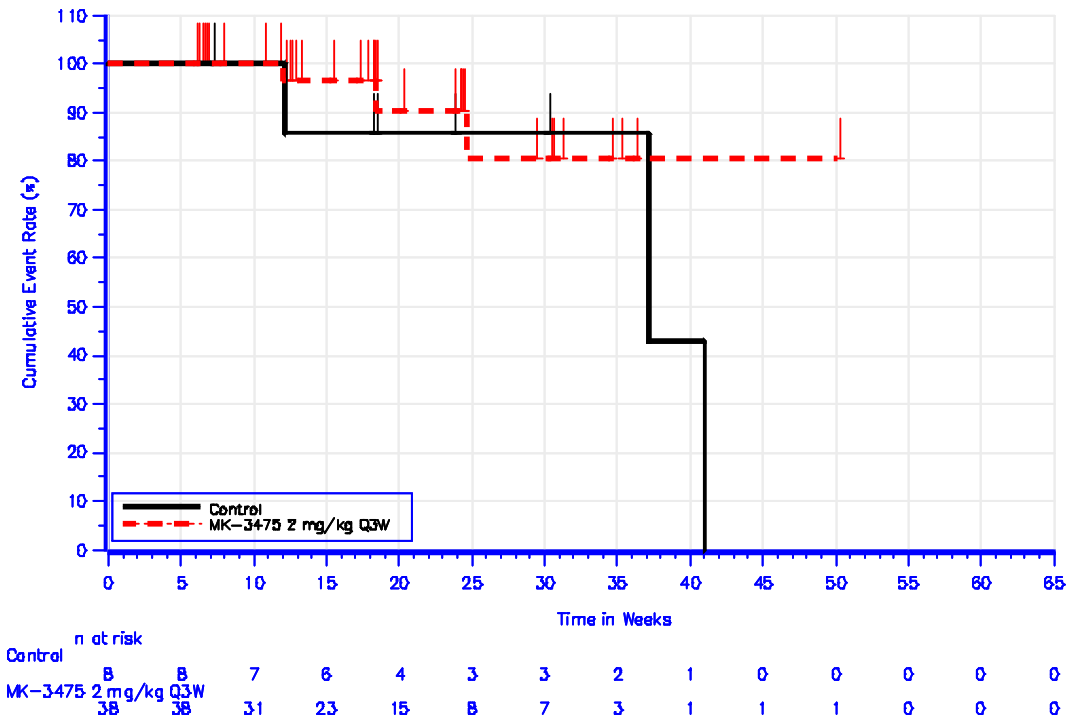
Table 29: KEYNOTE-002 - Summary of time to response & response duration for subjects with overall response based on central (IRO) review – ITT population

	Control n=179	Pembrolizumab 2 mg/kg Q3W

		n=180
Number of Subjects with Response†	8	38
Time to Response† (weeks)		
• **Mean (SD)**	14 (3)	16 (5)
• **Median (Range)**	13 (12-18)	13 (12-30)
Response Duration‡ (weeks)		
• **Median (Range)§**	37 (7+ - 41)	Not reached (6+ - 50+)
Number of Non-progressing (non-PD) Subjects (%)	5 (63)	35 (92)

† Analysis on time to response and response duration are based on subjects with a best overall response as confirmed complete response or partial response only.
‡ From product-limit (KM) method for censored data.
§ "+" indicates there is no progressive disease by the time of last disease assessment.

Figure 14: KEYNOTE-002 - KM estimates of overall response duration in subjects with confirmed response based on central (IRO) review – ITT population



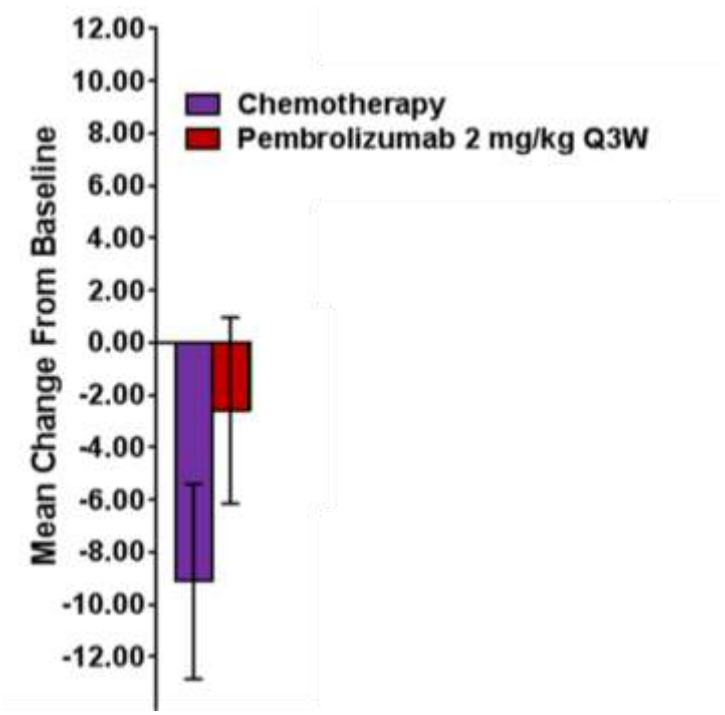
Exploratory endpoints

(HRQoL) changes: IA2 - Data cut-off 12 May 2014

Pembrolizumab resulted in significantly smaller changes from baseline in the global health status/quality of life scale of the EORTC QLQ-C30, as observed by a lower reduction in the least squares mean change from baseline.

The difference in least squares mean change from baseline at week 12 in HRQoL assessed with EORTC QLQ-C30 was 6.52 (P = 0.011) for pembrolizumab 2 mg/kg versus chemotherapy (Figure 15)

Figure 15: Global Health Status/Quality of Life Scale[a]



[a]A higher score denotes better HRQoL or function, and a higher negative score denotes worse HRQoL or functions.

The pembrolizumab treatment arm has a consistently smaller proportion of "deteriorated" and generally larger proportion of "stable" patients for global health status/quality of life, different functional scales and symptoms scales, when compared with the control arm.[20] Further details on HRQoL results are presented in section 5.4 and Appendix 20 of the submission.

KEYNOTE-001 - Part B2[18;65]: Data cut-off 18 October 2013

Clinical effectiveness results are presented in this section for pembrolizumab 2 mg/kg Q3W only (anticipated licence dose; and dosage relevant to this submission. Full results for both study arms (including pembrolizumab 10 mg/kg Q3W) are presented as an appendix (Appendix 6).

Summary

Primary efficacy analyses were based on the FAS population as was pre-specified in the protocol. Efficacy analyses were also conducted based on the APaT population. The FAS population differs from the APaT population by removing patients without a baseline measurable lesion by independent central review from the ORR analysis. Because these patients are incapable of achieving a partial response, the ORR in the FAS population provides a more representative estimation of the ORR for pembrolizumab.

A summary of the key efficacy endpoints concerning Part B2 of KEYNOTE-002 is provided in Table 30 below:

Table 30: Summary of key efficacy endpoints for pembrolizumab in advanced melanoma – KEYNOTE-001 Part B2 (Ipilimumab refractory population)

	2 mg/kg Q3W
Number of Patients (FAS/APaT)	81/89
BOR Analysis (IRO per RECIST 1.1)	
ORR – FAS % (95% CI)	26% (17, 37)
ORR – APaT % (95% CI)	24% (15, 34)
Response Duration[1] (IRO per RECIST 1.1, APaT Population)	
Median in weeks	Not Reached
% of responses ongoing among responders	86%
Median Time to Response in Weeks (range)	12 (11-36)
PFS (IRO per RECIST 1.1, APaT Population)	
Median in weeks (95% CI)	22 (12, 36)
24-week PFS rate	45%
PFS (IRO per irRC, APaT Population with Confirmed Responders)	
Median in weeks (95% CI)	36 (24, 46)
24-week PFS rate	62%
OS (APaT population)	

Median in months	13
6 month OS rate (%)	79%
12 month OS rate (%)	53%[2]

[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.
[2] Because of the small number of patients with survival follow-up beyond 6 months in Part B2, projections beyond 6 months are not reliable and should be interpreted cautiously

Efficacy results are presented in more detail below:

Primary endpoints

Response Rate (RR) – Part B2 FAS population

Best Overall Response (BOR) analysis as assessed by central review (IRO) using RECIST 1.1 is shown in Table 31 below. Confirmed responses were reported by independent central review in 26% (95% CI: 17-37%) of patients who were treated at 2 mg/kg Q3W. There was no apparent difference in response rate between those treated at the 2 mg/kg or 10 mg/kg dose (p=0.96), suggesting that doses of 2 mg/kg and 10 mg/kg given every 3 weeks produce comparable response rates in patients with advanced melanoma (see Appendix 6). Approximately 50% of patients treated with pembrolizumab 2 mg/kg achieved disease control, with a best response of stable disease or better. Assessment of tumour response based on the immune-related response criteria (irRC) as assessed by investigators is also summarised in Table 31 below:

Table 31: KEYNOTE-001 Part B2- Best overall response by independent central review and investigator[18]

	RECIST 1.1, independent central review	**IrRC, investigator review**
	Pembrolizumab 2mg/kg	**Pembrolizumab 2mg/kg**
Best overall response*	n=81	n=89
• **Complete response**	1 (1%)	3 (3%)
• **Partial response**	20 (25%)	21 (24%)
• **Stable disease**	20 (25%)	31 (35%)
• **Progressive disease**	27 (33%)	24 (27%)
• **Not evaluable[†]**	13 (16%)	--

• **No assessment‡**	--	10 (11%)
• **Overall response rate (95% CI)**	26% (17 to 37)	27% (18 to 37)

*RECIST 1.1=Response Evaluation Criteria In Solid Tumours (version 1.1). *Eight patients in each treatment group did not have measurable disease as per independent central review at baseline and were excluded from the analysis of best overall response as per RECIST by independent central review. †Patients who had no scans for response assessment or who had radiological images of non-diagnostic quality. ‡Patients who exited the study without post-baseline response assessment by the investigator. §Difference. Two-sided p values are provided for testing the null hypothesis that there is no difference in the response between groups versus there is a response difference.*

Secondary endpoints

Disease Control Rate (DCR), Response Duration, PFS and OS

DCR, response duration and PFS based on both irRC and RECIST 1.1 and OS served as secondary endpoints in this population. Analyses of PFS and OS were based on the APaT population that consists of all patients who received at least 1 dose of study treatment.

Analyses of DCR and response duration analysis based on confirmed responses from independent central review (IRO) assessment using RECIST 1.1 are summarised in Table 32 below.

Patients initiated treatment by 05-Apr-2013, and at the time of the data cut-off for this analysis (18-Oct-2013), had at least 28 weeks of follow-up since starting treatment for the analysis. About half (47%) of the B2 population initiated treatment by 11-Jan-2013 and thus had at least 9 months of follow-up.

There were 41 confirmed objective responses (in both treatment arms; i.e. 26%) in Part B2 patients, and the response durations ranged from 6+ to 37+ weeks at the time of the analysis. The median response duration for the population in Part B2 was not reached at the time of this analysis. The median time to response (representing the first assessment of objective response among confirmed objective responses) was approximately 12 weeks, corresponding to the time of the first scheduled disease assessment.

Results from investigator review based on irRC are also summarised in Table 32 below

Table 32: KEYNOTE-001 Part B2- Disease control rate and response duration

	RECIST 1.1, independent central review (IRO)	irRC, investigator review

	Pembrolizumab 2mg/kg	Pembrolizumab 2mg/kg
Disease control rate (95% CI)	51% (39 to 62)	62% (51 to 72)
Patients with response	n=21	n=24
• **Time to response (weeks): median (range)**	12 (11 to 36)	12 (11 to 24)
• **Response duration (weeks): median (range)**	NR (6–37¶)	NR (12–42¶)

NR=not reached; ¶Non-progressive disease or ongoing response at the last assessment. §Difference. Two-sided p values are provided for testing the null hypothesis that there is no difference in the response between groups versus there is a response difference

PFS (RECIST 1.1 and irRC) – based on APaT population

The primary method of analysis of PFS was based on RECIST 1.1measurements by independent central review (IRO assessment) in the APaT population. The results provide additional support for the clinical benefit of pembrolizumab treatment by showing that a significant portion of the study population achieves durable clinical benefit from pembrolizumab treatment and help provide a comprehensive assessment of clinical efficacy.

PFS for patients in Part B2 is shown in Table 33 below. At the time of this analysis, approximately 61-64% of the study population had experienced progression by independent central review or death. The median PFS for the 2 mg/kg Q3W treatment arm was 22 weeks.

The shape of the PFS curve (Figure 16) shows a sharp decline around week 12 at the time of the first imaging assessment, followed by a shallow decline thereafter, suggesting that a major proportion (30-40%) of the study population may achieve a long duration of PFS as the data from this cohort matures. By KM estimation, the 24-week progression-free rate (PFR) is 45% for the 2 mg/kg Q3W arm. The 24-week PFR is consistent with the rate of disease control in the best overall response analysis. Given the shape of the PFS curve, these data suggest that there is a relatively large (~10-20%) population of patients who do not achieve an objective response to pembrolizumab, but will derive clinical benefit from treatment. A summary of PFS as determined by investigator review per irRC is also summarised in Table 33 and

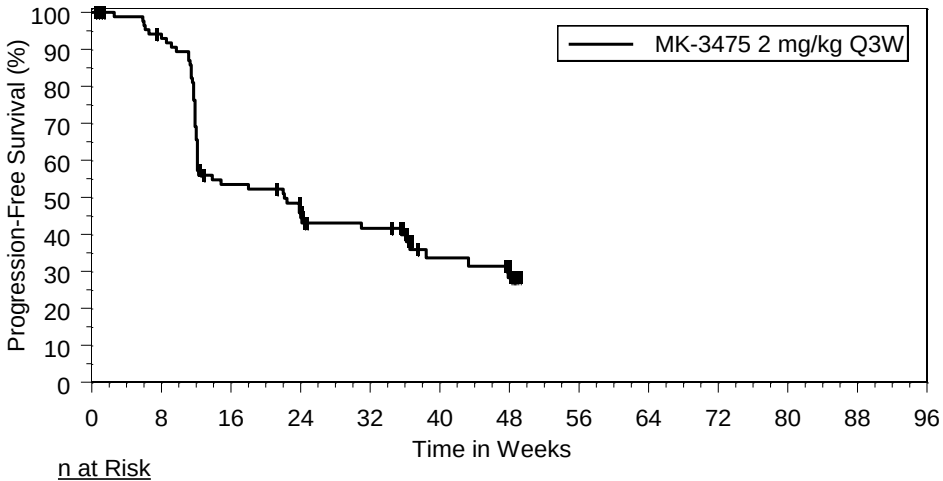
Figure 17 below. There are more progression events based on RECIST 1.1 than irRC generally due to new lesions, and therefore the median PFS is longer when progression is assessed by irRC and may be a better reflection of the benefit to patients.

Table 33: KEYNOTE-001 Part B2 - Summary of PFS based on (1) IRO assessment per RECIST 1.1 and (2) INV review per irRC –- APaT population

	RECIST 1.1, independent central review	irRC, investigator review
	Pembrolizumab 2mg/kg	**Pembrolizumab 2mg/kg**
PFS	n=89	n=89
• **Median (weeks; 95% CI)**	22 (12 to 36)	31 (22 to 48)
• **At 24 weeks (95% CI)**	45% (34 to 55)	57% (46 to 67)

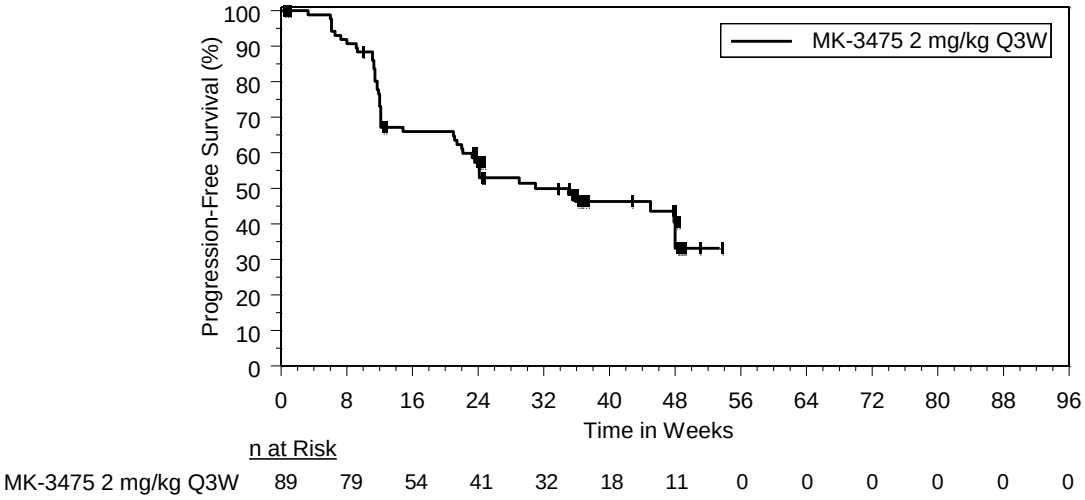
RECIST1.1=Response Evaluation Criteria In Solid Tumors (version 1.1). NR=not reached. ‖Hazard ratio.

Figure 16: KEYNOTE-001 Part B2 - KM estimates of PFS based on central (IRO) review per RECIST1.1



n at Risk													
MK-3475 2 mg/kg Q3W	89	79	43	34	28	15	7	0	0	0	0	0	0

Figure 17: KEYNOTE-001 Part B2 - KM estimates of PFS based on INV review per irRC



OS - based on APaT population

Overall survival for Part B2 patients is displayed in Table 34 and Figure 18. At the time of data analysis, there were 32 (36%) deaths in 89 patients across the pembrolizumab 2 mg/kg treatment arm.

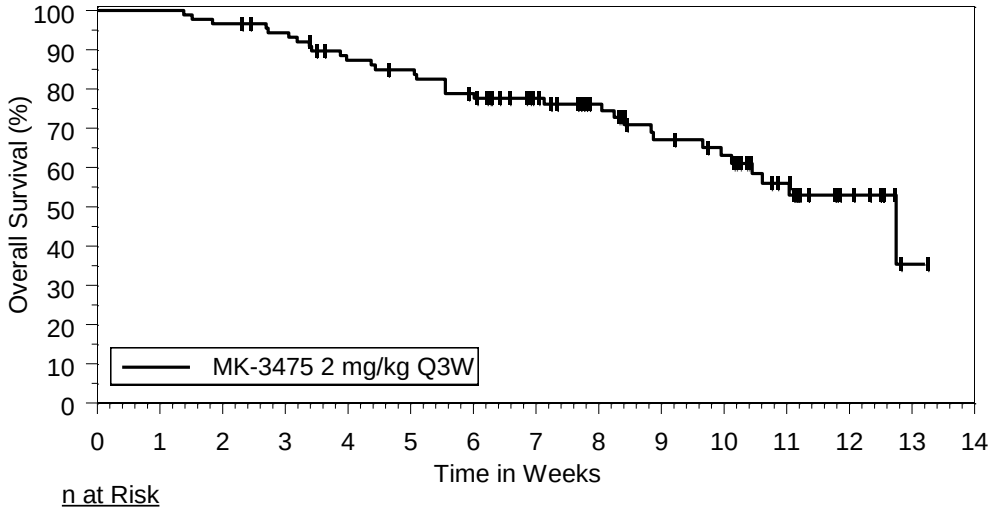
The median OS was 13 months (95% CI: 10 months to not estimable) for the 2 mg/kg Q3W arm, but it is important to note that there were very few patients at risk at this point in the KM estimate (only 9 patients at risk at 12 months and one patient at risk at 13 months), so the median is not a reliable estimate at the time of this analysis.

The 6-month OS rate (fraction of patients alive at 6 months) was approximately 79%. Due to heavy censoring, point estimates beyond 6 months have to be interpreted with caution.

Table 34: KEYNOTE-001 Part B2 - Summary of OS – APaT population

	Pembrolizumab 2mg/kg Q3W (N=89
Death (%)	32 (36.0)
Median survival (Months) §	12.7
95% CI for Median survival §	(10.1, --)
OS rate at 6 months in % §	78.8
OS rate at 12 months in % §	53.0
OS: Overall survival. † Based on Cox regression model with treatment as a covariate (Pembrolizumab 2 mg/kg Q3W versus Pembrolizumab 10 mg/kg Q3W). *§ From product-limit (KM) method for censored data.*	

Figure 18: KEYNOTE-001 Part B2 - KM estimates of OS – APaT population



n at Risk															
MK-3475 2 mg/kg Q3W	89	89	86	82	73	70	64	53	45	35	31	20	9	1	0

KEYNOTE-006[14]: Additional clinical data supporting the efficacy profile of pembrolizumab

Summary

KEYNOTE-006 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.

On 24 March 2015, MSD announced that KEYNOTE-006 had met its two primary endpoints of PFS and OS, and will 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 also published on the same day in the New England Journal of Medicine.[14] The study will continue safety and survival follow-up until the final analysis.

Methods

Key inclusion criteria were as follows:

- Histologically or confirmed diagnosis of unresectable stage III or IV melanoma

- Patients who had not received prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (1st line) or who had received one prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (2nd line) were both eligible.
- $BRAF^{V600}$ mutational status must have been know, although previous BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase levels and no clinically significant tumour-related symptoms / evidence of rapidly progressive disease.
- ECOG performance status 0 or 1
- Provision of a tumour sample adequate for assessing PD-L1 expression.

Key exclusion criteria:

- Patients who had received previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors and those who had ocular melanoma, active brain metastases, or a history of serious autoimmune disease.

Study design

In this phase 3 RCT, 834 patients with advanced melanoma were randomised in a 1:1:1 ratio to receive one of the following treatments regimens:

- Pembrolizumab 10 mg/kg Q2W
- Pembrolizumab 10 mg/kg Q3W
- Ipilimumab 3 mg/kg Q3W (maximum of four doses)

Randomisation was stratified according to line of therapy (1st line versus 2nd line), ECOG performance status (0 verses 1) and PD-L1 expression (positive versus negative).

Primary and secondary endpoints

The primary end points were PFS and OS. Secondary end points included ORR, duration of response, and safety. Efficacy was assessed in the ITT population. Safety was assessed in the APaT population.

Statistical analysis

The protocol specified the performance of two interim analyses: the first (IA1) was to be performed after at least 260 patients had disease progression or died in all study groups and all patients had been followed for at least 6 months. The primary objective of this analysis was to evaluate the superiority of either pembrolizumab regimen over ipilimumab for PFS at a one-

sided alpha level of 0.002. At IA1, OS was evaluated at a one-sided alpha level of 0.00002 to have a negligible effect on the overall type I error rate to preserve the alpha level for the IA2 and final analyses. IA2 was to be performed after at least 290 patients had died in all the study groups and all patients had been followed for at least 9 months or when the minimum follow-up duration was 12 months, whichever occurred first. The primary objective of IA2 was to evaluate the superiority of either pembrolizumab regimen over ipilimumab for overall survival at a one-sided alpha level of 0.005 with the use of the Hochberg step-up procedure.

Data presented below are from IA1, with the exception of OS which is from IA2.

Results:

During the period 18 Sep 2013 – 3 Mar 2014, 834 patients were enrolled in KEYNOTE-006 across 16 countries. 279 were randomly assigned to receive pembrolizumab Q2W, 277 to receive pembrolizumab Q3W, and 278 to receive ipilimumab. The disposition of patient flow from randomization through data read out following IA2 has been published.[14] Patient characteristics were well balanced across study groups, with no significant differences among the groups (Table 35).

Table 35: KEYNOTE-006: Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

	Pembrolizumab Q2W	Pembrolizumab Q3W	Ipilimumab
Characteristic	**(N = 279)**	**(N = 277)**	**(N = 278)**
Median age (range) — yr	61 (18–89)	63 (22–89)	62 (18–88)
Male sex — no. (%)	161 (57.7)	174 (62.8)	162 (58.3)
ECOG performance status — no. (%)			
• 0	196 (70.3)	189 (68.2)	188 (67.6)
• 1	83 (29.7)	88 (31.8)	90 (32.4)
Elevated baseline LDH level — no. (%)	81 (29.0)	98 (35.4)	91 (32.7)
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–positive tumour — no. (%)	225 (80.6)	221 (79.8)	225 (80.9)
BRAF ^{V600} mutation — no. (%)	98 (35.1)	97 (35.0)	107 (38.5)

Brain metastasis — no. (%)	23 (8.2)	27 (9.7)	28 (10.1)
Line of previous systemic therapy — no. (%)§			
• 0	183 (65.6)	185 (66.8)	181 (65.1)
• 1	96 (34.4)	91 (32.9)	97 (34.9)
Type of previous systemic therapy — no. (%)¶			
• Chemotherapy	36 (12.9)	41 (14.8)	29 (10.4)
• Immunotherapy	8 (2.9)	7 (2.5)	12 (4.3)
• BRAF or MEK inhibitor or both	50 (17.9)	45 (16.2)	56 (20.1)

- *Progression-free Survival : IA1 (data cut-off: 03 Sep 2014)*

On the basis of 502 events that were analysed at IA1, the two pembrolizumab regimens significantly prolonged PFS in the ITT population. Results are presented in Table 36 and

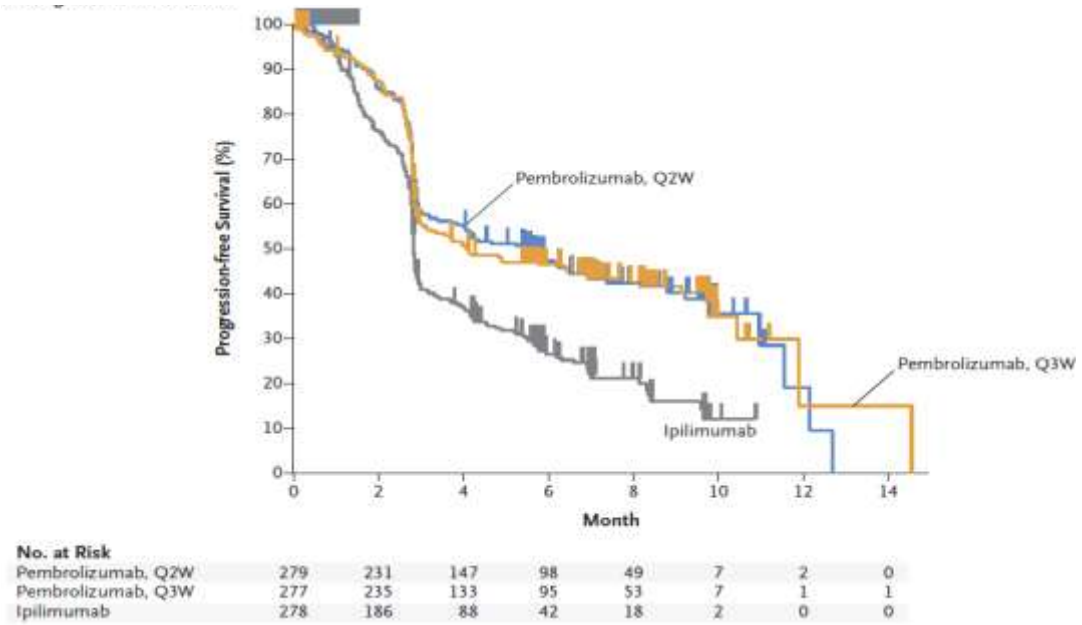
Figure 19 below. Based on their review of the results from IA1, the data and safety monitoring committee (DSMC) recommended that the study should continue as planned and unblind the results to select MSD representatives for regulatory purposes.

Table 36: KEYNOTE-006 IA1: PFS (ITT population)

Treatment	N	Median PFS (Months) (95% CI)	PFS rate at 6 Months in %	pembrolizumab vs. ipilimumab	
				Hazard Ratio (95% CI)	p-value
Ipilimumab 3 mg/kg	278	2.8 (2.8, 2.9)	26.5%		
Pembrolizumab 10 mg/kg Q2W	279	5.5 (3.4, 6.9)	47.3%	0.58 (0.46, 0.72)	P<0.001
Pembrolizumab 10 mg/kg Q3W	277	4.1 (2.9, 6.9)	46.4%	0.58 (0.47, 0.72)	P<0.001

The benefit for PFS was evident in all pre-specified subgroups for the two pembrolizumab groups (Fig. 2A). The benefit of pembrolizumab over ipilimumab was observed in both PD-L1–positive and PD-L1–negative subgroups, as compared with ipilimumab.

Figure 19: KEYNOTE-006: KM estimate of PFS[14] (rates at IA1 data cut-off: 03 Sep 2014)



- *Overall Survival - IA2 (data cut-off: 03 Mar 2015)*

At the time of data cut-off for IA2 (driven by a minimum follow-up duration of 12 months for all patients), 289 deaths had occurred. OS results are presented in Table 37 and Figure 20 below, which show that both pembrolizumab groups demonstrated a statistically significant superior OS result when compared to the ipilimumab group.

Because the OS results for the two pembrolizumab groups were superior to those for the ipilimumab group at the prespecified one-sided alpha level of 0.005 using the Hochberg step-up procedure, the independent DSMC recommended stopping the study early to allow patients in the ipilimumab group the option of receiving pembrolizumab.

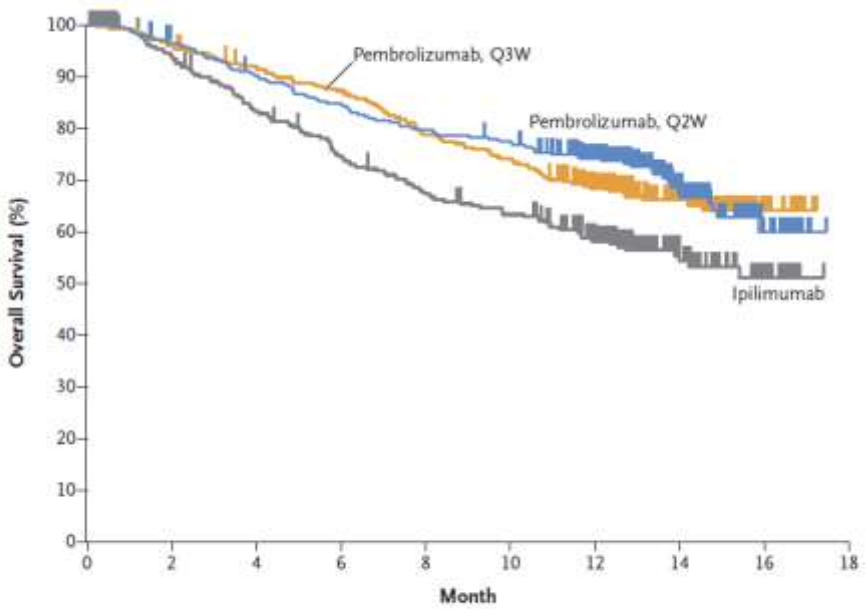
Final OS analysis will be performed after at least 435 deaths have occurred in all the study groups or when all patients have been followed for at least 21 months.

Table 37: KEYNOTE-006 IA2: OS (ITT population)

Treatment	N	One-year estimates of survival	Median OS (Months) (95% CI)	pembrolizumab vs. ipilimumab

		in %		Hazard Ratio (95% CI)	p-value
Ipilimumab 3 mg/kg	278	58.2%	not reached		
Pembrolizumab 10 mg/kg Q2W	279	74.1%	not reached	0.63 (0.47, 0.83)	P<0.0005
Pembrolizumab 10 mg/kg Q3W	277	68.4%	not reached	0.69 (0.52, 0.90)	P = 0.0036

Figure 20: KEYNOTE-006 KM estimate of OS[9] (rates at of IA2 data cut-off: 03 Mar 2015)



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

The pembrolizumab benefit was observed across all subgroups and for the two regimens,[9] with the exception of the PD-L1 negative tumours subgroup; however in this subgroup, the sample sizes were small, and the confidence intervals were wide.

Response Rates

Data on RRs are provided in Table 38 below.

Table 38: KEYNOTE-006 RR – IA1 (ITT population)

Treatment	Response rates (P value versus ipilimumab)	Rates of complete response	Median duration of response
Ipilimumab 3 mg/kg	11.9%	1.4%	not reached
Pembrolizumab 10 mg/kg Q2W	33.7% (P<0.001)	5.0%	not reached
Pembrolizumab 10 mg/kg Q3W	32.9% (P<0.001)	6.1%,	not reached

The results available from KEYNOTE-006 demonstrate that both regimens of pembrolizumab improved PFS and OS in patients with advanced melanoma when compared with ipilimumab. The relative risk of progression or death was decreased by 42%[9] with the two pembrolizumab regimens that were tested, and the relative risk of death was decreased by 31 to 37%.[9] Response rates significantly favoured pembrolizumab, and were consistent with previous findings for both pembrolizumab[18;69] and ipilimumab.[80] There were no apparent differences in efficacy between the two pembrolizumab regimens tested in this study. The lack of a dose–response relationship is consistent with the results from both KEYNOTE-001 and KEYNOTE-002. **In conclusion, this randomised study comparing two immune checkpoint inhibitors showed that pembrolizumab resulted in significantly prolonged PFS and OS when compared with ipilimumab.**

4.8 Subgroup analysis

KEYNOTE-002

A pre-specified secondary endpoint in KEYNOTE-002 was to evaluate OS, PFS, and ORR in the biomarker positive subgroup defined by PD-L1 expression level (cut-off point was defined and validated using data from the melanoma subjects in KEYNOTE-001 prior to any biomarker analysis in KEYNOTE-002) receiving either pembrolizumab or chemotherapy, as detailed below:

- ORR: Based on proportion of subjects with complete response (CR) or partial response (PR) based on confirmed central review assessment (IRO) using RECIST 1.1 criteria by PD-L1 expression level.

- PFS: Based on assessment of independent central review (IRO) using RECIST 1.1 by PD-L1 expression level from randomisation until progression or death due to any cause, whichever occurred first.
- OS: Based on time from randomisation to death due to any cause by PD-L1 expression level.

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.

While baseline characteristics were generally balanced between treatment arms in the PD-L1 positive subgroup, there was an imbalance in BRAF^{V600} mutation status and baseline lactate dehydrogenase (LDH) levels among the treatment arms in the PD-L1 negative subgroup.[20] There were more BRAF ^{V600} mutation positive subjects in the 2 mg/kg Q3W (36%) compared to the control group (18.9%). Yet there were also fewer BRAF ^{V600} mutation positive subjects in the 2 mg/kg Q3W (11%) arm in a subgroup of subjects with unknown PD-L1 status. Similarly, there were more subjects with elevated LDH in 2 mg/kg Q3W (43%) treatment arm compared to the control group (24%). Both BRAF ^{V600} mutation status and elevated LDH are poor prognostic factors, and the imbalance in these two baseline factors may have confounded the efficacy results of the PD-L1 negative subgroup. Nevertheless, the percent of patients who are PD-L1 negative and have a durable response is not insubstantial and there was evidence of efficacy for these patients compared with chemotherapy. In the setting of patients with few remaining good treatment options for melanoma, the clinical utility of this biomarker is questionable.

Subgroup analyses of PFS were also performed to further evaluate the treatment effect of pembrolizumab in various subgroups based on clinically relevant baseline subject or tumour characteristics. All subgroups except for baseline tumour size were pre-specified in the statistical analysis plan (SAP). In KEYNOTE-001, baseline tumour size had been found to be one of the most important predictive factors for efficacy and consequently, the subgroup analysis based on baseline tumour size was added in the current CSR.

The following factors were included for analysis: Sex (female vs. male); age category (≤65 vs. >65 years); race (white vs. non-white); region (US vs. ex-US); ECOG status (0 vs. 1); baseline LDH level (normal vs. elevated); BRAF mutation status (mutant vs. wild type); baseline tumour size measured by IRC (< Median in overall population vs. ≥ median in overall population); investigator's choice of chemotherapy recorded via IVRS prior to randomisation (types with >10% patients in the control group).

Efficacy was found to be consistent across all major demographic and prognostic subgroups.

Further details on subgroup analyses results are provided in Appendix 7.

KEYNOTE-001 Part B2[65]

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[74] in the APaT population.

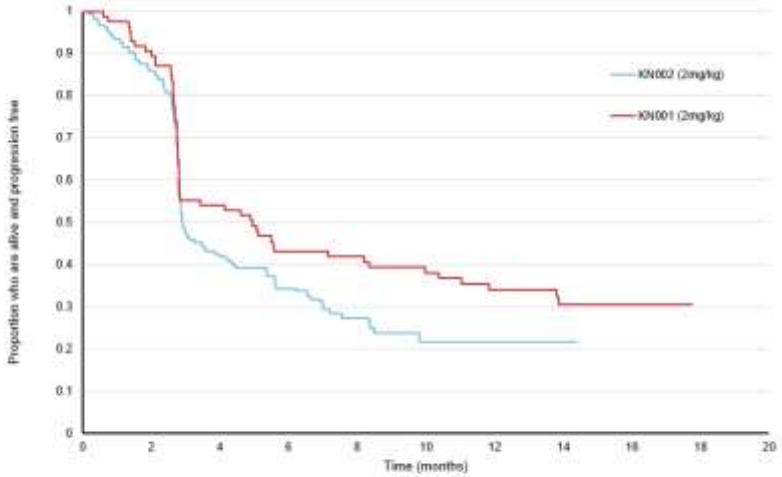
Subgroup analyses specifically in Part B2 were consistent with the conclusion that efficacy is consistent across all major baseline demographic and prognostic factors. Further details are provided in Appendix 7.

4.9 Meta-analysis

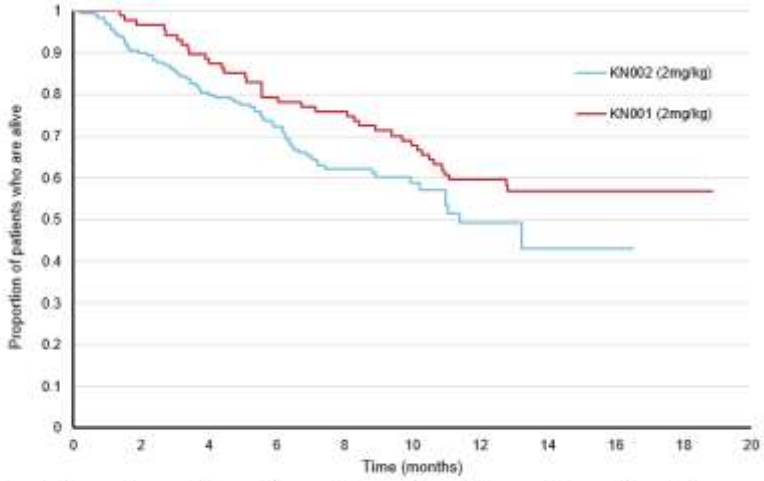
There is only one randomised controlled trial for the intervention versus a relevant comparator (KEYNOTE-002). KEYNOTE-001 Part B2 did not include a comparator of relevance to the decision problem. A meta-analysis was not conducted as it was not possible to pool the data on ipilimumab-refractory patients treated with pembrolizumab 2 mg Q3W in KEYNOTE-002 and with those from Part B2 of the KEYNOTE-001. This is because the treatment effect was found to be higher in patients assessed in Part B2 of the KEYNOTE-001 trial: PFS and OS absolute outcomes for both studies were too dissimilar (Figure 21).

These differences were attributed to dissimilarities between the trials in terms of study design and baseline characteristics of the included patients (with KEYNOTE-002 patients having a poorer prognosis than those included in KEYNOTE-001 in terms of poorer performance status and more severe metastases, as reported in Table 39 below. This led to the conclusion it would be inappropriate to pool data concerning pembrolizumab 2 mg/kg Q3W from KEYNOTE-002 and Part B2 of KEYNOTE-001.

Figure 21: PFS and OS KM curves (respectively) from KEYNOTE-002 and Part B2 KEYNOTE-001



Time (Months)	0	2	4	6	8	10	12	14	16
KN002	180	153	84	56	27	10	10	10	0
KN001	89	77	45	35	33	30	23	16	16



Time (Months)	0	2	4	6	8	10	12	14	16	18
KN002	180	161	143	120	81	40	22	7	0	0
KN001	89	85	76	69	66	58	51	40	40	40

Table 39: Comparison of baseline characteristics of patients receiving pembrolizumab 2mg in KEYNOTE-001 (Part B2) and KEYNOTE-002

	KEYNOTE-001 – Part B2			KEYNOTE-002			
	Pembro 2 Q3W	Pembro 10 Q3W	Total	Pembro 2 Q3W	Pembro 10 Q3W	Chemotherapy	Total
	n = 89	n = 84	N = 173	n = 180	n = 181	n = 179	N = 540
Age, median (range)	69.0 (18-88)	62.5 (27-86)	61.0 (18-88)	62.0 (15-87)	60.0 (27-89)	63.0 (27-87)	61.5 (15-89)
Male	53.9%	67.9%	60.7%	58%	60%	64%	61%
ECOG PS							
0	66%	68%	67%	54%	54%	55%	55%
1	34%	32%	33%	44%	46%	45%	45%
BRAF status							
Mutant	24%	22%	23%	24%	22%	23%	23%
Wild type	76%	78%	77%	76%	78%	77%	77%
LDH level							
Normal	55%	58%	58%	55%	58%	60%	58%
Elevated (≥110% ULN)	43%	40%	40%	43%	40%	38%	40%
M stage							
M0	15.7%	11.9%	13.9%	1%	<1%	<1%	<1%
M1a	7.9%	13.1%	10.4%	8%	5%	7%	7%
M1b	15.7%	15.5%	15.6%	8%	12%	9%	10%
M1c	57.3%	56.0%	56.6%	83%	82%	83%	83%

4.10 Indirect and mixed treatment comparisons

The comparators of relevance to the decision problem are BSC and dacarbazine.

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 8. An additional search was conducted encompassing a wider list of interventions, to ascertain whether it was possible to conduct an indirect comparison of pembrolizumab relative to BCS in the absence of direct head to head data. Further details of the search strategy are provided in Appendix 8.

4.10.2: Details of treatments

The decision problem identifies dacarbazine and BSC as relevant comparators to pembrolizumab in the population of interest. An additional search was also conducted including additional interventions (vemurafenib, dabrafenib, nivolumab, temozolomide) outside of the named interventions list, to assess the potential inclusion based on network strengthening of an indirect comparison against BSC.

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 40 below:

Table 40: Criteria used in the trial selection process

	Inclusion	Exclusion
Population	Patients with unresectable stage III or IV melanoma previously treated with ipilimumab	Patients with non-cutaneous melanoma (i.e. ocular or mucosal melanoma) and with unknown primary site
Interventions	Pembrolizumab DTIC; other chemotherapy Best supportive care* Additionally a separate search was conducted including the following interventions for the purpose of assessing the possibility of conducting an indirect comparison against BSC: Vemurafenib Dabrafenib Nivolumab Temozolomide	Any other intervention
Comparisons	Any of the interventions listed above, other interventions that have been compared to at least two of the interventions above, best supportive care	Any other comparison

Outcomes	At least one of the following outcomes: Overall response (OR) Progression-free survival (PFS) Overall survival (OS)	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 (RCTs)	Non-randomised clinical trials, prospective and retrospective observational studies, case studies
Language restrictions	English	Any other language
**This intervention may be assessed in either ipilimumab-naïve or ipilimumab experienced populations*		

4.10.4: Summary of trials

Table 41: Summary of the trials

References of trial	Pembrolizumab	Chemotherapy	BSC
KEYNOTE -001 (Part B2)[65]	✓		
KEYNOTE-002[20]	✓	✓	
Hofmann et al 2011[12]		✓	✓
Eisen et al 2010[13]		✓	✓

KEYNOTE-002 provides comparative efficacy data for pembrolizumab with chemotherapy regimens, including dacarbazine.

The currently available evidence base does not include a trial that evaluates pembrolizumab 2 mg/kg relative to BSC among ipilimumab experienced patients. Furthermore, there is no trial that compares chemotherapy with BSC in this population.

One RCT comparing second-line chemotherapy (lenalidomide) plus BSC and BSC alone among advanced melanoma patients not exposed to ipilimumab was identified.[13] The results of this trial suggest that chemotherapy in addition to BSC, after failure of 1st line systemic treatment, demonstrates no benefit in terms of tumour response, time to progression, or overall survival.

The literature search also identified a prospective non-randomised study evaluating BSC with or without 2nd line chemotherapy.[12] Although this study did not meet the selection criteria due to study design, it was included in the review. The results of this study indicate that chemotherapy is unlikely to have any survival benefit over BSC in patients with advanced

metastatic melanoma. Extrapolation of this lack of efficacy among patients not previously treated with ipilimumab to patients previously treated with (i.e. refractory to) ipilimumab, suggests that the chemotherapy arm of KEYNOTE-002 can be considered a proxy for BSC regarding expected OS and PFS. This argument is further justified by the fact that there are no RCTs demonstrating an improvement in survival with dacarbazine relative to BSC / any other control agent.[11] Dacarbazine is mostly used in a palliative setting outside of clinical trials.[11]

Given these findings, an indirect comparison of pembrolizumab with BSC was not conducted.

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

Full details can be found in Appendix 9.

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 42 below.

Table 42: 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[65;69]	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[69] CLINICAL STUDY REPORT P001 V01[65]	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 43 below.

Table 43: Summary of trial methodology

Trial number (acronym)	KEYNOTE-001 – Part B1[65;69]
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,[65;69] 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.[69] 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[73] (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[74] (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 44 below.

Table 44: Characteristics of participants in the Part B1 across treatment groups[65]

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 • M1c • Unknown	11 (27) 20 (49) 2 (5)	3 (19) 8 (50) 0	7 (29) 9 (38) 0	5 (16) 18 (56) 2 (6)	2 (9) 18 (82) 0	28 (21) 73 (54) 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[65;69] has been assessed using the Newcastle-Ottawa Scale,[81] which was identified in a previous systematic review[82] 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 45 below, with full details provided in Appendix 10.

Table 45: 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)[69]

Response to therapy was evaluated using the following two criteria:

- Investigator-assessed per immune-related response criteria (irRC):[73] designed to analyse the response to immunotherapy agent
- Independent, central radiologic review per RECIST 1.1:[74] 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.[73] The confirmed response rate across all doses, as assessed by central review according to RECIST 1.1,[74] 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[74] 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 22). Responses did not vary according to prior exposure to ipilimumab (Table 46 and Figure 22).

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[74] are shown in Figure 23. 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[74] 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.

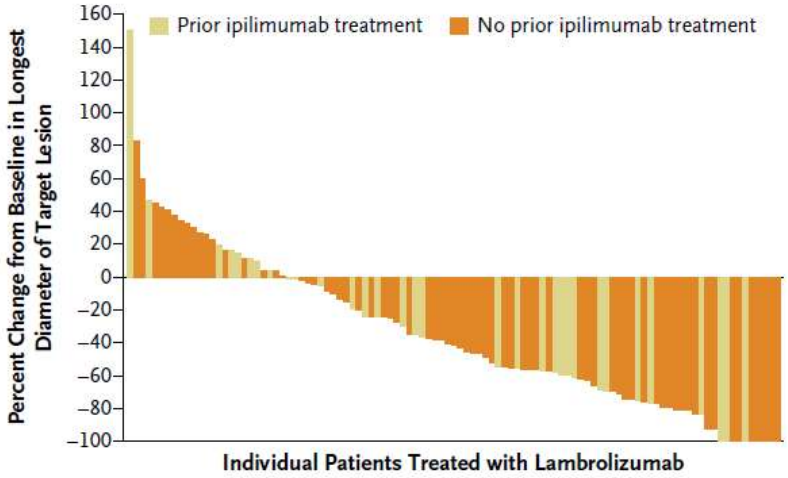
Table 46: KEYNOTE 001 Part B1:ORR according to dosing regimen and status with respect to prior therapy with ipilimumab, as assessed according to RECIST1.1 and irRC[69]

Pembrolizumab	RECIST	Immune-Related Response (irRC)

Regimen and Ipilimumab Status						
	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])

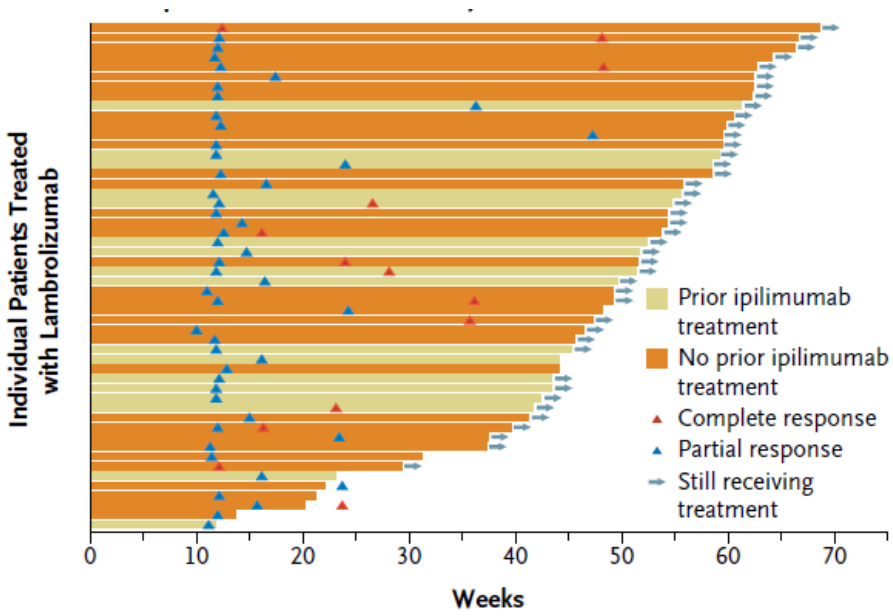
† Duration of response was defined as the time from the first response to the time of documented progression or, in the case of censored data, the most recent tumour assessment. All the lower and upper ranges listed are for censored data and refer to the time from the first response to the most recent 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 22: Anti-tumour activity of pembrolizumab – Best Objective Response[69]



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 23: Time to response and duration of study treatment[69]



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-002: Adverse reactions[20]

As per information regarding clinical efficacy results, the safety results provided in the main body of this submission focus on the anticipated licence dose of pembrolizumab (2 mg/kg). Results including the 10 mg/kg pembrolizumab study arm are included as an Appendix for completeness (see Appendix 13).

The All Patients as Treated (APaT) population was used for the analysis of safety data in KEYNOTE-002. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required.

In the primary safety comparison between pembrolizumab and control, subjects who crossed over to pembrolizumab were censored at time of crossover (i.e., adverse events [AEs] that occurred during treatment with pembrolizumab were excluded).

Safety and tolerability were assessed by clinical and statistical review of adverse events (AEs) and laboratory values reported during the treatment period up to the data cut-off of 12-May-2014.

AE summary counts and listing tables provided include AEs from the first dose of study medication to 30 days following the last dose of study medication if the subject was discontinued from study treatment, or prior to the first dose of pembrolizumab if the subject crossed over, or up to the data cut-off date of 12-May-2014 if the subject is still on study treatment.

Serious adverse event (SAE) counts include events from the first dose out to 90 days following the last dose of study medication for subjects discontinued from study treatment to account for the extended safety follow-up period for SAEs per protocol.

A summary of exposure and AEs is provided in Table 47 below:

Table 47: KEYNOTE-002 – Summary of exposure and AEs[20;68]

	Pembrolizumab 2 mg/kg Q3W n = 178	Chemotherapy n = 171
Exposure, days		
• **Median (range)**	112.5 (1-499)	61 (1-335)
• **Mean (SD)**	144.2 (107.7)	75.5 (66.4)
With one or more AEs	172 (96.6%)	167 (97.7%)
Grade 3-5 AE	83 (46.6%)	88 (51.5%)
Any grade drug-related AE	121 (68.0%)	138 (80.7%)
Drug-related Grade 3-5 AE	20 (11.2%)	45 (26.3%)
Serious AE	79 (44.4%)	57 (33.3%)
Serious drug-related AE	14 (7.9%)	17 (9.9%)
Death	11 (6.2%)	8 (4.7%)
Drug-related AE leading to death	1 (0.6%)	0 (0.0%)
AE leading to discontinuation	18 (10.1%)	20 (11.7%)
Drug-related AE leading to discontinuation	5 (2.8%)	10 (5.8%)
Serious AE leading to discontinuation	15 (8.4%)	14 (8.2%)
Serious drug-related AE leading to discontinuation	5 (2.8%)	4 (2.3%)

In the pembrolizumab 2 mg/kg Q3W arm, the most common AEs, occurring in a total of at least 15% of subjects, were fatigue (38.8%), pruritus (23.5%) constipation (21.3%), diarrhoea (20.8%), nausea (19.7%), anaemia (17.4%), cough (17.4%), decreased appetite (16.3%), and arthralgia (15.2%).

In the chemotherapy arm, the most common AEs, occurring in a total of at least 15% of subjects, were fatigue (48.0%), nausea (41.5%), anaemia (26.3%), vomiting (22.8%), decreased appetite (22.8%), constipation (20.5%), alopecia (20.5%), diarrhoea (19.9%), and cough (15.8%).

The number and percentage of subjects with AEs (incidence ≥10% in one or more treatment group, regardless of causality) in the APaT population is presented in tabulated format in Appendix 11 (Table 1).

Table 48[20] displays the number and percentage of subjects with Grade 3-5 AEs (incidence ≥1% in one or more treatment group) in the APaT population. Overall, at least one Grade 3-5 AE was reported for 46.6% of subjects who received pembrolizumab 2 mg/kg Q3W. Overall, the most common Grade 3-5 AEs, occurring in 2% or more subjects who received 2 mg/kg Q3W, were

anaemia (7.9%), fatigue (3.4%), hyponatremia (3.4%), dehydration (2.8%), and generalized oedema (2.2%).

In the chemotherapy control arm, at least one Grade 3-5 AE was reported by 51.5% of subjects. Overall, the most common Grade 3-5 AEs, occurring in 2% or more of subjects, were anaemia (6.4%), fatigue (6.4%), pulmonary embolism (4.1%), thrombocytopenia (4.1%), leukopenia (3.5%), neutropenia (3.5%), neutrophil count decreased (3.5%), platelet count decreased (3.5%), nausea (2.9%), vomiting (2.9%), sepsis (2.9%), diarrhoea (2.3%), white blood cell count decreased (2.9%), dyspnea (2.9%), constipation (2.3%), and pneumonia (2.3%).

Table 48: KEYNOTE-002 - Subjects with grade 3-5 AEs (incidence ≥ 1% in one or more treatment groups) (APaT population)[20]

	Control		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	N	(%)
Subjects in population	171		178	
• with one or more adverse events	88	(51.5)	83	(46.6)
• with no adverse events	83	(48.5)	95	(53.4)
Blood and lymphatic system	**22**	**(12.9)**	**14**	**(7.9)**
• Anaemia	11	(6.4)	14	(7.9)
• Febrile neutropenia	3	(1.8)	0	(0.0)
• Leukopenia	6	(3.5)	0	(0.0)
• Neutropenia	6	(3.5)	0	(0.0)
• Thrombocytopenia	7	(4.1)	0	(0.0)
Cardiac disorders	**4**	**(2.3)**	**2**	**(1.1)**
Endocrine disorders	**0**	**(0.0)**	**2**	**(1.1)**
• Hypopituitarism	0	(0.0)	0	(0.0)
Eye disorders	0	(0.0)	2	(1.1)
Gastrointestinal disorders	**20**	**(11.7)**	**19**	**(10.7)**
• Abdominal pain	2	(1.2)	**3**	**(1.7)**
• Ascites	1	(0.6)	2	(1.1)
• Colitis	1	(0.6)	0	(0.0)
• Constipation	4	(2.3)	1	(0.6)
• Diarrhoea	4	(2.3)	1	(0.6)
• Nausea	5	(2.9)	2	(1.1)
• Vomiting	5	(2.9)	3	(1.7)
General disorders and administration site conditions	**18**	**(10.5)**	**18**	**(10.1)**
• Asthenia	3	(1.8)	3	(1.7)
• Chest Pain	0	(0.0)	2	(1.1)
• Death	1	(0.6)	3	(1.7)
• Fatigue	11	(6.4)	6	(3.4)
• General physical health • deterioration	3	(1.8)	2	(1.1)
• Generalised oedema	1	(0.6)	4	(2.2)
• Oedema peripheral	0	(0.0)	0	(0.0)
Hepatobiliary disorders	**1**	**(0.6)**	**4**	**(2.2)**
• Cholecystitis	0	(0.0)	2	(1.1)

Infections and infestations	**20**	**(11.7)**	**18**	**(10.1)**
• Bronchitis	0	(0.0)	2	(1.1)
• Erysipelas	**2**	**(1.2)**	1	(0.6)
• Pneumonia	**4**	**(2.3)**	1	(0.6)
• Sepsis	**5**	**(2.9)**	1	(0.6)
• Skin infection	0	(0.0)	2	(1.1)
• Urinary tract infection	2	(1.2)	2	(1.1)
• Viral infection	0	(0.0)	2	(1.1)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**4**	**(2.2)**
Investigations	**21**	**(12.3)**	**7**	**(3.9)**
• Blood alkaline phosphatase increased	1	(0.6)	2	(1.1)
• Haemoglobin decreased	3	(1.8)	0	(0.0)
• Lymphocyte count decreased	3	(1.8)	1	(0.6)
• Neutrophil count decreased	6	(3.5)	0	(0.0)
• Platelet count decreased	6	(3.5)	0	(0.0)
• White blood cell count decreased	5	(2.9)	1	(0.6)
Metabolism and nutrition disorders	**13**	**(7.6)**	**18**	**(10.1)**
• Cachexia	0	(0.0)	2	(1.1)
• Decreased appetite	1	(0.6)	0	(0.0)
• Dehydration	1	(0.6)	5	(2.8)
• Hyperglycaemia	3	(1.8)	1	(0.6)
• Hypoalbuminaemia	1	(0.6)	2	(1.1)
• Hypokalaemia	2	(1.2)	2	(1.1)
• Hyponatraemia	2	(1.2)	6	(3.4)
Musculoskeletal and connective tissue disorders	**7**	**(4.1)**	**5**	**(2.8)**
• Arthralgia	2	(1.2)	1	(0.6)
• Back pain	3	(1.8)	0	(0.0)
• Musculoskeletal pain	1	(0.6)	2	(1.1)
• Myalgia	1	(0.6)	2	(1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**(1.8)**	**5**	**(2.8)**
Nervous system disorders	**7**	**(4.1)**	**10**	**(5.6)**
• Brain oedema	0	(0.0)	0	(0.0)
• Neuropathy peripheral	2	(1.2)	0	(0.0)
• Syncope	2	(1.2)	3	(1.7)
Psychiatric disorders	**2**	**(1.2)**	**5**	**(2.8)**
• Confusional state	0	(0.0)	2	(1.1)
• Mental status changes	0	(0.0)	2	(1.1)
Renal and urinary disorders	**2**	**(1.2)**	**1**	**(0.6)**
Respiratory, thoracic and mediastinal disorders	**17**	**(9.9)**	**10**	**(5.6)**
• Dyspnoea	5	(2.9)	2	(1.1)
• Pleural effusion	3	(1.8)	3	(1.7)
• Pneumonitis	0	(0.0)	0	(0.0)
• Pulmonary embolism	7	(4.1)	3	(1.7)

Skin and subcutaneous tissue disorders	**2**	**(1.2)**	**4**	**(2.2)**
Vascular disorders	**5**	**(2.9)**	**5**	**(2.8)**
• Hypertension	1	(0.6)	0	(0.0)
• Hypotension	1	(0.6)	2	(1.1)

Adverse events considered "possibly," "probably," or "definitely" related to study medication by the Investigator are combined into the category of drug-related AEs. The incidence of drug-related AEs was 68.0% in subjects treated with pembrolizumab 2 mg/kg Q3W. In the pembrolizumab 2 mg/kg Q3W arm, the most common AEs, occurring in a total of at least 15% of subjects, were fatigue (22.5%) and pruritus (20.8%). While fatigue was a common drug-related AE in subjects receiving pembrolizumab, fatigue was more frequent in subjects who received chemotherapy. In the chemotherapy control arm, the incidence of drug-related AEs was 80.7%. Among subjects in this arm, the most common AEs, occurring in a total of at least 15% of subjects, were fatigue (36.3%), nausea (32.7%), anaemia (20.5%), alopecia (20.5%), vomiting (15.2%), and decreased appetite (15.2%). Tabulated details concerning subjects with drug-related AEs (incidence ≥ 10% in one or more treatment groups) are available in Appendix 11 (Table 2).

The number of subjects with drug-related Grade 3-5 AEs (incidence ≥1% in one or more treatment group) in the APaT population is displayed in Table 49 below. Overall the incidence of drug-related Grade 3-5 AEs was 11.2% in the pembrolizumab 2 mg/kg arm. The most common drug-related Grade 3-5 AEs in the 2 mg/kg Q3W arm, occurring in a total of at least 1% of subjects, were: fatigue (1.1%), generalized oedema (1.1%), and myalgia (1.1%). In contrast, in the chemotherapy control arm, the overall incidence of drug-related Grade 3-5 AEs was higher, at 26.3%, and the most common drug-related Grade 3-5 AEs in subjects receiving chemotherapy were cytopenias, nausea, vomiting, diarrhoea, and fatigue. AEs that are higher (by at least 2%) for chemotherapy compared to the pembrolizumab arm include: cytopenias (anaemia, leukopenia, and neutropenia), fatigue, investigations associated with cytopenias (neutrophil count, leukocyte count, and platelet count decreased), and the gastrointestinal system organ class. There were no drug-related Grade 3-5 AEs that were increased by at least 2% for the pembrolizumab arm compared to chemotherapy.

Table 49: KEYNOTE-002 - Subjects with Grade 3-5 drug-related AEs (incidence ≥ 1% in one or more treatment groups (APaT population)[20]

	Control		**Pembrolizumab 2 mg/kg Q3W**	
	n	**(%)**	**N**	**(%)**
Subjects in population	171		178	

• with one or more adverse events	45	(26.3)	20	(11.2)
• with no adverse events	126	(73.7)	158	(88.8)
Blood and lymphatic system	**17**	**(9.9)**	**1**	**(0.6)**
• Anaemia	9	(5.3)	1	(0.6)
• Febrile neutropenia	2	(1.2)	0	(0.0)
• Leukopenia	6	(3.5)	0	(0.0)
• Neutropenia	6	(3.5)	0	(0.0)
• Thrombocytopenia	4	(2.3)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**1**	**(0.6)**
Hypopituitarism	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**9**	**(5.3)**	**5**	**(2.8)**
• Colitis	0	(0.0)	0	(0.0)
• Diarrhoea	3	(1.8)	0	(0.0)
• Nausea	4	(2.3)	0	(0.0)
• Vomiting	4	(2.3)	1	(0.6)
General disorders and administration site conditions	**10**	**(5.8)**	**6**	**(3.4)**
• Fatigue	8	(4.7)	2	(1.1)
• Generalised oedema	0	(0.0)	2	(1.1)
Hepatobiliary disorders	**0**	**(0.0)**	**1**	**(0.6)**
Infections and infestations	**4**	**(2. 3)**	**0**	**(0.0)**
Investigations	**13**	**(7.6)**	**2**	**(1.1)**
• Lymphocyte count decreased	2	(1.2)	1	(0.6)
• Neutrophil count decreased	5	(2.9)	0	(0.0)
• Platelet count decreased	5	(2.9)	0	(0.0)
• White blood cell count • Decreased	4	(2.3)	0	(0.0)
Metabolism and nutrition disorders	**3**	**(1.8)**	**1**	**(0.6)**
• Decreased appetite	0	(0.0)	0	(0.0)
• Hyponatraemia	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**2**	**(1.2)**	**2**	**(1.1)**
• Myalgia	1	(0.6)	2	(1.1)
Nervous system disorders	**3**	**(1.8)**	**0**	**(0.0)**
• Neuropathy peripheral	2	(1.2)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**2**	**(1.1)**
• Pneumonitis	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(0.6)**	**2**	**(1.1)**
(Database Cut-off Date: 12MAY2014).				

Potentially immune-related AEs (irAEs) are defined as AEs of unknown etiology that are temporally associated with drug exposure and are consistent with an immune phenomenon. The primary method of assessing potentially immune related AEs for this study is the analysis of adverse events of special interest (AEOSI), which is based on an analysis of a list of preferred AE terms of potential immune etiology based on ongoing monitoring of the pembrolizumab safety profile during the development program. The list of terms is intentionally broad in an attempt to capture all informative data, and therefore not all reported events are likely to be

immune mediated. The list of terms is updated periodically based on emerging pembrolizumab safety data.

An overview of the number and percentage of subjects with any AEOSI in the APaT population is presented in Table 50 below. Overall, 16.3% of subjects on the 2 mg/kg Q3W pembrolizumab treatment arm were reported to have any AEOSI at the time of this analysis. Most of the AEOSIs were Grade 1-2 in severity, with 5 subjects (2.8%) on the 2 mg/kg Q3W arm experiencing Grade 3 or Grade 4 AEOSIs. There were no fatal AEOSIs. Relatively few subjects in the pembrolizumab 2 mg/kg arm discontinued treatment due to an AEOSI: 1.1% (2 out of 178). AEOSIs and irAEs showed a similar profile with respect to all categories of AEs in the pembrolizumab arms. As expected, the frequency of AEOSIs was lower on the chemotherapy control arm, with 1.8% of subjects experiencing any AEOSI, and one subject (0.6%) with a Grade 3 or higher AEOSI. Table 51 displays the number and percentage of subjects with AEOSIs (incidence >0% in one or more treatment groups)

Table 50: KEYNOTE-002 – AE summary – AEOSI (APaT population)[20]

	Pembrolizumab 2 mg/kg Q3W n = 178	Chemotherapy n = 171
With one or more AEs	29 (16.3%)	3 (1.8%)
Grade 3-5 AE	5 (2.8%)	1 (0.6%)
Any grade drug-related AE	23 (12.9%)	0 (0.0%)
Drug-related Grade 3-5 AE	4 (2.2%)	0 (0.0%)
Serious AE	8 (4.5%)	2 (1.2%)
Serious drug-related AE	6 (3.4%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)
Drug-related AE leading to death	0 (0.0%)	0 (0.0%)
AE leading to discontinuation	2 (1.1%)	1 (0.6%)
Drug-related AE leading to discontinuation	2 (1.1%)	0 (0.0%)
Serious AE leading to discontinuation	2 (1.1%)	1 (0.6%)
Serious drug-related AE leading to discontinuation	2 (1.1%)	0 (0.0%)

Table 51: KEYNOTE-002: Subjects with AEs (incidence >0% in one or more treatment groups) – AEOSI (APaT population)[20]

	Control		Pembrolizumab 2 mg/kg Q3W	
	N	(%)	N	(%)
Subjects in population	171		178	

with one or more adverse events	3	(1.8)	29	(16.3)
with no adverse events	168	(98.2)	149	(83.7)
Endocrine disorders	**1**	**(0.6)**	**18**	**(10.1)**
Adrenocortical insufficiency acute	0	(0.0)	1	(0.6)
Autoimmune thyroiditis	0	(0.0)	0	(0.0)
Hyperthyroidism	0	(0.0)	7	(3.9)
Hypophysitis	0	(0.0)	1	(0.6)
Hypopituitarism	0	(0.0)	0	(0.0)
Hypothyroidism	1	(0.6)	11	(6.2)
Thyroiditis	0	(0.0)	0	(0.0)
Eye disorders	**0**	**(0.0)**	**0**	**(0.0)**
Iritis	0	(0.0)	0	(0.0)
Uveitis	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**1**	**(0.6)**	**3**	**(1.7)**
Colitis	1	(0.6)	2	(1.1)
Pancreatitis	0	(0.0)	1	(0.6)
Hepatobiliary disorders	**1**	**(0.6)**	**2**	**(1.1)**
Autoimmune hepatitis	0	(0.0)	2	(1.1)
Hepatitis	1	(0.6)	0	(0.0)
Nervous system disorders	**0**	**(0.0)**	**0**	**(0.0)**
Myasthenic syndrome	0	(0.0)	0	(0.0)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(0.6)**
Tubulointerstitial nephritis	0	(0.0)	1	(0.6)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**3**	**(1.7)**
Interstitial lung disease	0	(0.0)	0	(0.0)
Pneumonitis	0	(0.0)	3	(1.7)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**2**	**(1.1)**
Erythema multiforme	0	(0.0)	0	(0.0)
Rash maculo-papular	0	(0.0)	1	(0.6)
Stevens-Johnson syndrome	0	(0.0)	1	(0.6)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**
Vasculitis	0	(0.0)	0	(0.0)

Selected AEs of potential immune etiology were pre-specified in KEYNOTE-002 including:

1) Grade ≥3 Diarrhoea and Grade ≥2 colitis

2) Grade ≥3 Hyperthyroidism, hypophysitis, and hypothyroidism

3) Grade ≥2 Pneumonitis, and

4) Grade ≥3 Rash

Table 52 shows a comparison of the incidence of these selected AEs between the pembrolizumab treatment and chemotherapy control arm, with 95% confidence intervals and p-values.

Table 52: KEYNOTE 002 - Analysis of AE summary – selected AEs of potential immune etiology (APaT population)[20]

		Difference in % vs. Control	
Treatment	**n (%)**	**Estimate (95% CI)**	**p-value**
Subjects in the population			
Control	171		
Pembrolizumab 2mg/kg Q3W	178		
Grade ≥ 3 Diarrhoea and Grade ≥ 2 colitis			
Control	5 (2.9)		
Pembrolizumab 2mg/kg Q3W	3 (1.7)	-0.8 (-6.2, 3.9)	0.688
Grade ≥ 3 Hyperthyroidism, hypophysitis, and hypothyroidism			
Control	0 (0.0)		
Pembrolizumab 2mg/kg Q3W	1 (0.6)	1.8 (-2,8, 6.4)	0.317
Grade ≥ 2 Pneumonitis			
Control	0 (0.0)		
Pembrolizumab 2mg/kg Q3W	0 (0.0)	0.0 (-3.3, 3.2)	>0.999
Grade ≥ 3 Rash			
Control	0 (0.0)		
Pembrolizumab 2mg/kg Q3W	0 (0.0)	0.0 (-3.3, 3.2)	>0.999

KEYNOTE-001 Part B2: Adverse reactions[18;65]

A summary of adverse events concerning the 2 mg/kg Q3W treatment arm of KEYNOTE-001 (Part B2) is provided in Table 53 below:

Table 53: KEYNOTE-001 Part B2 - Summary of AEs in the pembrolizumab 2mg/kg treatment arm[18]

	Pembrolizumab 2 mg/kg (n=89)
Drug-related adverse events	
Total	73 (82%)
Grade 3 or 4	13 (15%)
Serious	7 (8%)
Immune-related adverse events	
Grade 3 or 4	1 (1%)
Serious	3 (3%)
Adverse events of special interest	
Grade 3 or 4	4 (4%)
Drug-related, grade 3 or 4	3 (3%)
Serious	4 (4%)
Adverse events leading to discontinuation of drug*	
Total	6 (7%)
Drug-related, any grade	5 (6%)

Drug-related, grade 3 or 4	2 (2%)
Immune-related	3 (3%)
Of special interest	3 (3%)
Grade 3 or 4 drug-related adverse events occurring in one or more patients	
Fatigue	5 (6%)
Amylase increased	1 (1%)
Anaemia	1 (1%)
Autoimmune hepatitis	1 (1%)
Confusion	1 (1%)
Diarrhoea	0
Dyspnoea	0
Encephalopathy	1 (1%)
Hypophysitis	1 (1%)
Hypoxia	0
Muscular weakness	1 (1%)
Muscoloskeletal pain	0
Pancreatitis	0
Peripheral motor neuropathy	1 (1%)
Pneumonitis	1 (1%)
Rash	0
Rash maculopapular	0

Safety finding from KEYNOTE-001 (Part B2) show that pembrolizumab was generally well tolerated in this population of patients who had received previous treatment with melanoma. Overall, the safety profiles were similar between the pembrolizumab 2 mg/kg and 10 mg/kg groups (see Appendix 13). Drug-related adverse events occurred in 73 (82%) patients in the pembrolizumab 2 mg/kg group (Table 54); however, drug-related grade 3 or 4 adverse events occurred in only 13 (15%) patients treated at this dose. Fatigue was the only drug-related grade 3 to 4 adverse event that occurred in more than one patient (five [6%]; Table 54).

Only seven (8%) patients treated with pembrolizumab 2 mg/kg Q3W had drug-related serious adverse events and five (6%) discontinued treatment because of drug-related adverse events. There were no drug-related deaths reported. Potentially immune-mediated adverse events were generally manageable with treatment interruption and corticosteroid treatment, with only three patients discontinuing because of adverse events that were immune related or of special interest (Table 53).

Table 54: KEYNOTE-001 Part B2 - Drug-related AEs that occurred in ≥1% of all treated patients[18]

	2 mg/kg Q3W n=89	
Adverse event	**Any grade, n (%)**	**Grade 3–4, n (%)**
Any	73 (82)	13 (15)
Blood and lymphatic system disorders		
Anaemia	3 (3·4)	1 (1·1)
Thrombocytopenia	0 (0·0)	0 (0·0)
Ear and labyrinth disorders		

Vertigo	0 (0·0)	0 (0·0)
Endocrine disorders		
Hyperthyroidism	1 (1·1)	0 (0·0)
Hypophysitis	2 (2·2)	1 (1·1)
Hypothyroidism	5 (5·6)	0 (0·0)
Eye disorders		
Dry eye	2 (2·2)	0 (0·0)
Visual impairment	2 (2·2)	0 (0·0)
Gastrointestinal disorders		
Abdominal discomfort	2 (2·2)	0 (0·0)
Abdominal pain	3 (3·4)	0 (0·0)
Constipation	4 (4·5)	0 (0·0)
Diarrhoea	10 (11·2)	0 (0·0)
Dry mouth	0 (0·0)	0 (0·0)
Gastro-oesophageal reflux disease	3 (3·4)	0 (0·0)
Nausea	7 (7·9)	0 (0·0)
Vomiting	2 (2·2)	0 (0·0)
General disorders and administrative site conditions		
Asthenia	5 (5·6)	0 (0·0)
Chest pain	0 (0·0)	0 (0·0)
Chills	7 (7·9)	0 (0·0)
Face oedema	2 (2·2)	0 (0·0)
Fatigue	29 (32·6)	5 (5·6)
Influenza-like illness	1 (1·1)	0 (0·0)
Mucosal inflammation	1 (1·1)	0 (0·0)
Peripheral oedema	4 (4·5)	0 (0·0)
Pain	2 (2·2)	0 (0·0)
Pyrexia	3 (3·4)	0 (0·0)
Infections and infestations		
Influenza	1 (1·1)	0 (0·0)
Laboratory abnormalities		
ALT increased	4 (4·5)	0 (0·0)
AST increased	3 (3·4)	0 (0·0)
Blood TSH decreased	0 (0·0)	0 (0·0)
Blood TSH increased	1 (1·1)	0 (0·0)
Thyroxine decreased	1 (1·1)	0 (0·0)
Weight decreased	3 (3·4)	0 (0·0)
Metabolism and nutrition disorders		
Decreased appetite	8 (9·0)	0 (0·0)
Dehydration	1 (1·1)	0 (0·0)
Musculoskeletal and connective tissue disorders		
Arthralgia	11 (12·4)	0 (0·0)
Back pain	3 (3·4)	0 (0·0)

Joint swelling	0 (0·0)	0 (0·0)
Muscle spasms	2 (2·2)	0 (0·0)
Muscular weakness	3 (3·4)	1 (1·1)
Myalgia	5 (5·6)	0 (0·0)
Pain in jaw	1 (1·1)	0 (0·0)
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)		
Tumour pain	1 (1·1)	0 (0·0)
Nervous system disorders		
Dizziness	2 (2·2)	0 (0·0)
Headache	4 (4·5)	0 (0·0)
Hypoesthesia	3 (3·4)	0 (0·0)
Lethargy	4 (4·5)	0 (0·0)
Peripheral neuropathy	1 (1·1)	0 (0·0)
Paraesthesia	0 (0·0)	0 (0·0)
Respiratory, thoracic, and mediastinal disorders		
Cough	8 (9·0)	0 (0·0)
Dyspnoea	7 (7·9)	0 (0·0)
Dyspnoea exertional	1 (1·1)	0 (0·0)
Pneumonitis	2 (2·2)	1 (1·1)
Wheezing	0 (0·0)	0 (0·0)
Skin and subcutaneous skin disorders		
Dry skin	2 (2·2)	0 (0·0)
Erythema	4 (4·5)	0 (0·0)
Night sweats	4 (4·5)	0 (0·0)
Pigmentation disorder	2 (2·2)	0 (0·0)
Pruritus	23 (25·8)	0 (0·0)
Rash	16 (18·0)	0 (0·0)
Rash generalised	1 (1·1)	0 (0·0)
Rash maculopapular	2 (2·2)	0 (0·0)
Skin hypopigmentation	0 (0·0)	0 (0·0)
Vitiligo	8 (9·0)	0 (0·0)

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 12).

Table 55 below provides details of the drug-related AEs according to dosing cohort[69] 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 55: 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

KEYNOTE-006: Additional data supporting the safety profile of pembrolizumab [9]

AE findings from IA1 of KEYNOTE-006 have recently been published.[9] The safety profile of pembrolizumab was similar to that in previous studies reported earlier in this submission, with no unexpected safety concerns and few grade 3 to 5 treatment-related adverse events reported to date. Despite exposure to treatment being approximately 3 times as long 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 adverse event.

In conclusion, this randomized study comparing two immune checkpoint inhibitors showed that pembrolizumab, as compared with ipilimumab resulted in fewer high-grade toxic events in patients with advanced melanoma.

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

Safety data from KEYNOTE-002 demonstrates an overall favourable safety profile for pembrolizumab as an immune therapy for advanced melanoma. This trial also demonstrates a favourable safety profile for pembrolizumab compared to chemotherapy.

AEOSIs were low in severity and generally reversible by withholding treatment and use of corticosteroids. The incidence of most AE categories was similar, or lower, on pembrolizumab, regardless of dosage, compared with chemotherapy, despite the longer duration of treatment for subjects on pembrolizumab. Grade 3-5 AEs in this trial occurred at a higher frequency in the control arm than previously reported in single-agent chemotherapy studies; more than 70% of subjects received 2 or more lines of prior therapy, and approximately 50% received prior chemotherapy.

Overall, the pembrolizumab safety profile during this study was similar to what one would expect in an advanced melanoma population, and build on the safety findings seen in KEYNOTE-001 Part B2. The safety analyses demonstrate that pembrolizumab is well tolerated and the safety profile is acceptable for an advanced melanoma population, when compared to chemotherapy. Therefore, from a safety perspective, pembrolizumab compares favourably to chemotherapy in subjects with advanced melanoma that progressed after ipilimumab.

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

Results from the second interim analysis (IA2) of KEYNOTE-002 show that treatment with pembrolizumab 2 mg/kg resulted in a statistically significant improvement in the primary endpoint of PFS relative to chemotherapy control, in patients with ipilimumab refractory advanced melanoma. The hazard ratio is 0.57 in the pembrolizumab 2 mg/kg Q3W arm over the control arm (one-sided p-value is <0.0001). The PFS improvement demonstrated is supported by a greater than 4-fold increase in ORR and a longer duration of responses. KEYNOTE-002 results presented for ORR and duration of response are corroborated by results presented for Part B2 of KEYNOTE-001.

Based on previous results with immunotherapies, it is likely that the median is not the best reflection of the magnitude of PFS improvement with pembrolizumab, potentially underestimating the true benefit. The PFS curves from KEYNOTE-002 converged at the median, which was reflective of the first scheduled scan after 12 weeks in both the pembrolizumab 2 mg/kg Q3W and chemotherapy control treatment arms. However, the curves showed a separation in the 3-month PFS results: 47.5% (95% CI; 40.0, 54.7) in the pembrolizumab 2 mg/kg arm compared to 35% (95% CI; 27.9, 42.2) in the control arm. The curves remained separate at 6 and 9 months, as reflected by a 6-month PFS rate of 34.3% (95% CI; 27.4, 41.3) in the pembrolizumab 2 mg/kg arm compared to 15.6% (95% CI; 10.5, 21.5) in the control arm, and a 9-month PFS rate of 23.7% (95% CI; 17.0, 31.1) in the pembrolizumab 2 mg/kg arm compared to 8.0% in the chemotherapy control arm (95% CI; 4.0, 13.9).

OS data presented from KEYNOTE-002 IA2 demonstrates a numeric trend in favour of pembrolizumab in spite of a 48% crossover rate. However, due this high level of crossover, the difference was not statistically significant. The final overall survival analysis will be performed after 370 deaths have occurred.

In line with DSU recommendations,[76] a variety of statistical modelling approaches were implemented to estimate the actual chemotherapy-related OS in the absence of crossover; these included the protocol pre-specified RPSFT method, the two-stage and IPCW methods. With this comprehensive analysis, we are able to better understand the better understand the chemotherapy-related OS in the absence of crossover. Based on the trial characteristics, the switching mechanism, the proportion of patients switching and the clinical validity of the outputs obtained, the two-stage adjustment was found to be the most appropriate method for this adjustment (see section 5.3.2). After the two-stage adjustment, pembrolizumab was shown to result in a statistically significant improvement in OS compared to the adjusted control arm (see sections 4.7 and 5.3.2),

Pembrolizumab 10 mg/kg Q3W efficacy data is presented in an appendix (Appendix 6). Efficacy of pembrolizumab is comparable between the anticipated licence dose of 2 mg/kg Q3W, and the 10 mg/kg Q3W dose levels for treating patients with advanced melanoma.

Efficacy of pembrolizumab 2mg/kg Q3W was found to be consistent across all major demographic and prognostic subgroups. 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 subjects compared with the overall population, which is consistent with the mechanism of action of an anti-PDL1 agent; however, although the rate of unknown PD-L1 results is substantial, in this setting of patients with few remaining good treatment options, the clinical utility of this biomarker is questionable.

According to the limited evidence evaluating 2nd line chemotherapy versus BSC among ipilimumab-naïve patients, there is no difference in overall survival between these two intervention strategies. Under the assumption that these findings also apply to the population of patients previously treated with ipilimumab, one may conclude that the relative efficacy of pembrolizumab versus chemotherapy according to KEYNOTE-002 in terms of PFS and OS also apply to a comparison of pembrolizumab with BSC.

The safety profile of pembrolizumab, when administered at 2 mg/kg Q3W, is favourable when compared to chemotherapy. In KEYNOTE-002, mean duration of study treatment was

nearly 2-fold (or more) longer on pembrolizumab compared to chemotherapy: mean exposure to pembrolizumab 2 mg/kg Q3W was 144 days versus 75 days in the chemotherapy control arm. Crude percentages of AEs are therefore likely to underestimate the differences in safety in favour of the control arm. Despite this, drug-related Grade 3-5 AEs were numerically higher in the chemotherapy control arm (26.3% in the control arm vs. 11.2% in the pembrolizumab 2 mg/kg Q3W arm). The overall frequency of AEs that are potentially immune-related was low (16.3% in the pembrolizumab 2 mg/kg arm). Immune-related AEs were typically Grade 1-2 in severity, and were generally reversible with treatment discontinuation and use of corticosteroids. The safety profile was not notably different between subjects who received 2 mg/kg Q3W compared to 10 mg/kg Q3W (results presented in Appendix 13).

In the context of another type of immunotherapy for melanoma, Grade 3-4 drug-related AEs occurred in 30/131 (22.9%) of subjects treated with ipilimumab[80] [16.1.12.16] compared to 11% of the 178 subjects who received pembrolizumab at the 2 mg/kg Q3W dose in KEYNOTE-002. In studies with ipilimumab, Grade 3-5 immune related AEs were reported in ~16% (21/131) subjects, and death due to drug-related AEs were reported in ~3% (4/131) [16.1.12.16] [16.1.12.41].[80;83] In KEYNOTE-002, Grade 3-5 AEOSIs occurred in 3% of subjects receiving pembrolizumab 2 mg/kg, and there were no treatment-related deaths. It is important to note that these are cross study comparisons, and definitions of immune relatedness differed, and based on narratives, AEOSIs may overestimate the frequency of immune-related adverse events; however, in all these analyses, the rates of Grade 3-5 AEs with pembrolizumab appears favourable compared to ipilimumab. Thus, pembrolizumab compares favourably to ipilimumab from a safety perspective, especially in light of the longer duration on study therapy.

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-002 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. KEYNOTE-002 was designed and powered to allow each pembrolizumab arm (2 mg/ kg Q3W and 10 mg/kg Q3W) to independently demonstrate significant benefit versus investigator choice chemotherapy (see section 4.4.1).

The definition of progression when evaluating the co-primary endpoint of PFS in KEYNOTE-002 followed an established response evaluation criteria (RECIST 1.1) in the primary efficacy analysis, in line with European guidance.[84]

PFS is not influenced by the implementation of crossover, which is commonly mandated by Ethics Committees,[85] and therefore features in many oncology trial designs. European Guidelines[84] acknowledge that one-way crossover to the experimental arm after disease progression is likely to hamper any subsequent comparisons of the two treatment arms in terms of OS when standard statistical methods of analysis, such as ITT are applied.[86] Yet the implementation of crossover within the study design of KEYNOTE-002 was considered necessary so as not to deprive subjects in the control arm from receiving a potentially more effective therapy from the pembrolizumab arm of KEYNOTE-002.

The confounding effect of crossover makes an analysis of OS based on non-adjusted data unreliable, and potentially underestimates the likely survival benefit associated with pembrolizumab. To control for this, a variety of crossover adjustments were implemented to estimate the actual chemotherapy-related OS in the absence of crossover. The RPSFT method had been pre-specified in the KEYNOTE-002 study protocol to adjust for the anticipated crossover effect in advance of the availability of trial based information needed to determine the clinical validity of the approach, which should be assessed *a posteriori*., such as crossover characteristics, trial size, and available data.[86] Nevertheless, following the NICE DSU[76] recommendations for the adjustment of crossover in clinical trials, additional validated and recommended crossover adjustments (two-stage and the IPCW) were implemented to estimate the actual chemotherapy-related OS in the absence of crossover. Based on the trial characteristics, the switching mechanism, the proportion of patients switching and the clinical validity of the outputs obtained, the two-stage adjustment was found to be the most appropriate method for this adjustment (see section 5.3.2).

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 EuroQoL EQ-5D according to the NICE reference case, in addition to the cancer specific EORTC-QLQC30.

Part B2 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 pembrolizumab 2 mg/kg and pembrolizumab 10 mg/kg.

External validity

The clinical trials for pembrolizumab, KEYNOTE-002 and KEYNOTE-001 (Part B2), although not conducted in the UK, were conducted in a patient population comparable with those patients experiencing the highest unmet need in England and Wales (those who have progressed following prior therapy with ipilimumab and if BRAF mutation positive, a BRAF or MEK inhibitor). Both of the above mentioned trials assessed pembrolizumab at the anticipated licensed dosage and treatment frequency (2 mg/kg Q3W). The frequency of administration and the duration of the pembrolizumab IV infusion (30 minutes) is comparable with the majority of chemotherapy treatment regimens currently administered to patients with advanced melanoma,

The patient characteristics of those with advanced melanoma in the UK have been previously reported,[87] but it is important to note that the majority of those patients included were generally receiving first-line therapy. Consequently the poorer prognosis of patients based on patient demographics that was seen in the KEYNOTE-002 trial population are unsurprising, given these patients are more heavily pre-treated. The patients included in KEYNOTE-002 are likely to have received more lines of therapy than those who would be expected to receive pembrolizumab in UK clinical practice. Approximately half of the patients enrolled in KEYNOTE-002 had received prior chemotherapy, whereas within UK practice, it is expected that pembrolizumab would be used prior to chemotherapy treatment where possible. In addition, it was a requirement that patients enrolled in KEYNOTE-002 must have experienced disease progression within 24 weeks of their last of 2 doses of ipilimumab to qualify for study inclusion. Greater survival than that seen in KEYNOTE-002 is expected to be observed when expanding the use of pembrolizumab to the wider, eligible population in UK clinical practice, as discussed in section 5.3.1.

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 56 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 56: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Patients with metastatic melanoma have a median survival of up to nine months[77-79]
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 a median extension to life of 3.5 months (based on two-stage crossover adjustment approach) and a mean extension to life of 1.59 years (projected from cost-effectiveness model) – see sections 4.7 and 5.3.2)
The treatment is licensed or otherwise indicated for small patient populations	The estimated number of patients eligible for pembrolizumab is expected to be approximately (628 in 2015,and approximately 300 annually thereafter - see Table 5 and sections 3.4 and 6 of submission.[88]

4.14 Ongoing studies

It is anticipated that Final Analysis data from KEYNOTE-002 will be available in Q4 2015. Given the study design and significant levels of crossover, we do not anticipate that this will demonstrate OS results which differ significantly from those presented in this submission based on IA2.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

Identification of 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 previously treated 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 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 57 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 19 and Appendix 22.

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 19 and Appendix 22 and are detailed in section 5.4.

Table 57: Inclusion and exclusion criteria for cost-effectiveness studies

Criteria	Inclusion	Exclusion	Rationale
Population	Patients with advanced melanoma previously treated 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.*			

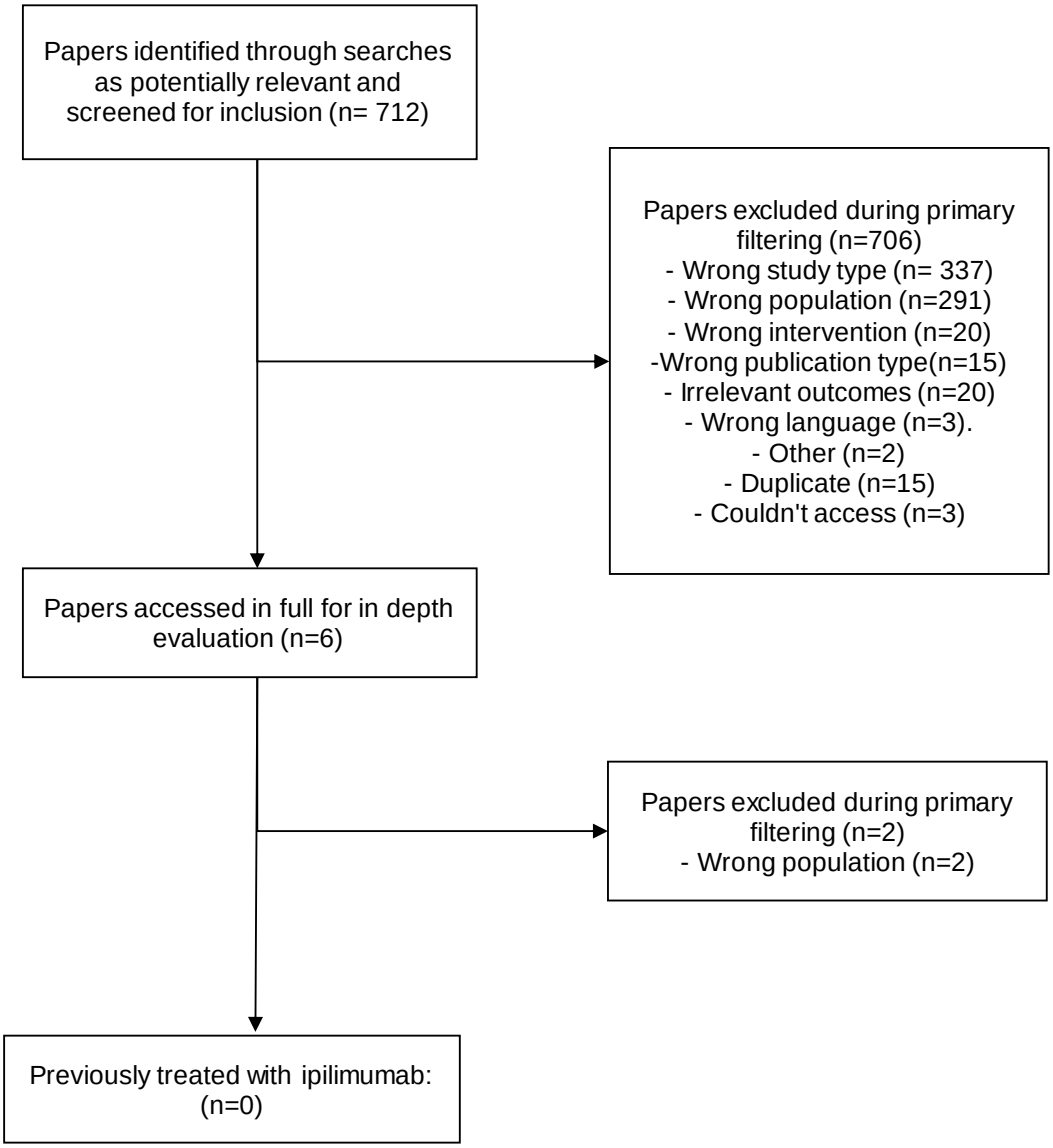
The above searches were conducted following the methodology for systematic review developed and published in 2009 by the Centre for Reviews and Dissemination (University of York).[89]

Description of identified studies

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

A total of 712 papers were identified in the cost-effectiveness search. No cost-effectiveness studies assessing patients previously treated with ipilimumab were found that met all the inclusion criteria (see Figure 24).

Figure 24: PRISMA diagram CEA studies



A summary list of published cost-effectiveness studies has not been compiled as no cost-effectiveness studies on patients previously treated with ipilimumab that met all the inclusion criteria were identified. The lack of identified cost-effectiveness studies in the ipilimumab previously treated 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).[2]

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 consisted of patients with unresectable or metastatic melanoma that had been previously treated with ipilimumab, and with a BRAF inhibitor if the patients were BRAF^{V600} mutation positive. This is in line with the anticipated licence indication and differs slightly from the population defined in the final appraisal scope with regards to patients with BRAF^{V600} positive mutations having had to receive both ipilimumab and a BRAF inhibitor prior to receiving pembrolizumab.

The main body of clinical evidence for pembrolizumab was derived from the KEYNOTE-002 trial, in which patients included had received at least two doses of ipilimumab and had experienced progressive disease within 24 weeks of the last dose of ipilimumab. In addition, patients who were BRAF^{V600} mutation positive had also received a prior treatment that included an approved BRAF and/or MEK inhibitor.[20;71] The justification for the choice of clinical evidence used in the economic model is presented in section 5.3.1. In this section the impact on outcomes from considering evidence derived from KN002 was assessed and it was concluded that the projected OS may have underestimated the total OS of patients treated with pembrolizumab as for the anticipated licence.

The baseline characteristics of the patients included in the model are presented in Table 58.

Table 58. Baseline characteristics of patients include in the model

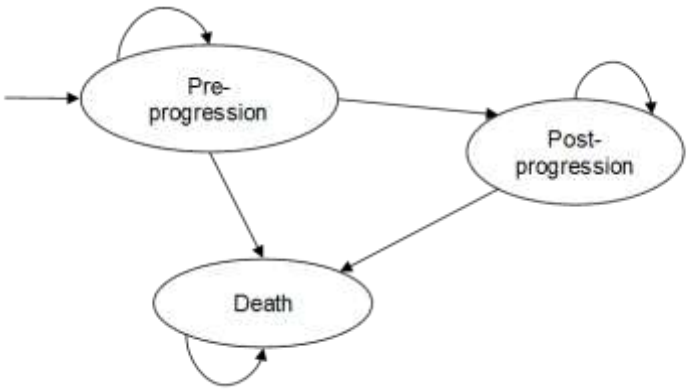
Patient Characteristics	Mean	Distribution	Reference / Source
Average age	59.99	Normal (59.99, 0.67)	KEYNOTE-002
Proportion male	0.6074	Beta (218.1, 140.9)	KEYNOTE-002
proportion ECOG 1	0.445	Beta (159.8, 199.2)	KEYNOTE-002
proportion ECOG2	0	Beta (0, 359)	KEYNOTE-002
Proportion brain metastases	0	Beta (0, 359)	KEYNOTE-002
proportion stage III	0.0335	Beta (12, 347)	KEYNOTE-002
proportion stage IV	0.933	Beta (334.9, 24.1)	KEYNOTE-002
proportion m1b	0.1031	Beta (37, 322)	KEYNOTE-002
proportion m1c	0.8215	Beta (294.9, 64.1)	KEYNOTE-002

5.2.2 Model structure

Based upon the previous cost-effectiveness models submitted to NICE within advanced melanoma, a de-novo economic analysis was built as a 'partitioned-survival' model that compared two treatment arms, including pembrolizumab and best supportive care (BSC). Consistent with the majority of economic models previously developed for NICE oncology submissions in advanced melanoma[1;15;16] the model consisted of three health states: pre-progression, post-progression and death (see Figure 25). This approach was also in line with the clinical endpoints assessed in the pembrolizumab clinical trials, in which OS and PFS were either primary[20;71] or secondary endpoints.[65;70] 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. [1;15;16]

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 25. Model structure

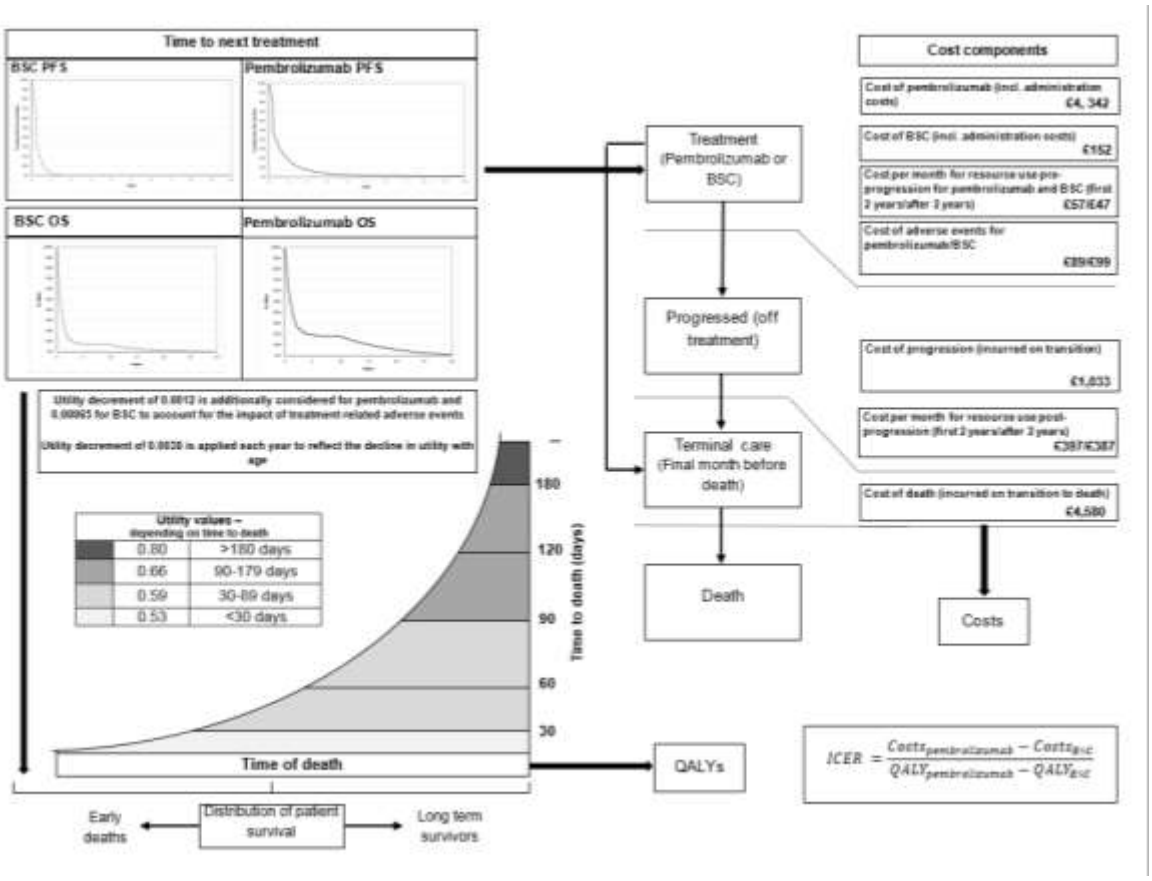


The partitioned-survival model was developed by fitting survival curves to trial data for progression free survival (PFS) and overall survival (OS). Instead of using transition probabilities (as would be the case with Markov models), the health transitions were derived from the proportion of patients that were reflected by the areas under the PFS and OS curves. 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 were identified by the patients located underneath the PFS curve. The area between the PFS and the OS represented the proportion of post-progression patients, i.e. those who were in the 'post progression' health state.

In the model, patients were assumed to receive treatment until progression, in line with the anticipated licence for pembrolizumab. This is also consistent with the protocol of the KEYNOTE-002 trial, where patients remained on treatment until progression or the occurrence of a serious adverse event resulting in discontinuation.[20;71] Treatment switches to subsequent therapies other than pembrolizumab were not included in the model as the use of other subsequent therapies was low and relatively balanced between the treatment arms.

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 26), 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.[2] The use of time-to-death sub-health states was implemented considering four health states: <30 days to death, 30-89 days to death, 90-179 days to death and >180 days to death), each associated with a specific utility value. Additionally, each of the non-absorbing health states had specific treatment, resource utilisation and adverse event costs.

Figure 26. 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 reasonable assumption given that patients eligible for pembrolizumab should have previously received treatment with ipilimumab (and a BRAF and/or a MEK inhibitor if the patient was $BRAF^{V600}$ mutation positive) and, therefore, the only subsequent remaining treatment administered in UK clinical practice would be systemic therapy (i.e. mostly dacarbazine), which has not demonstrated an improvement in OS when compared to BSC without systemic therapy (see sections 4.10.4 and 5.2.4 for further details).

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-002 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.[74]
- 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 59: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	30 years	Lifetime horizon for the defined target population[90] (1.1% of patients alive after this period) In line with previous advanced melanoma submissions[1;15;16]
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[1;2;15;16]
Half-cycle correction	Not applied to costs and health effects in the base case but in sensitivity analysis	Irrelevant, given cycle length[15;16]

Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case[90]
Discount of 3.5% for utilities and costs	Yes	NICE reference case[90]
Perspective (NHS/PSS)	Yes	NICE reference case[90]
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 anticipated licence and dose (i.e. 2 mg/kg as an IV infusion over 30 minutes every 3 weeks [Q3W]).

BSC was considered to be the most appropriate comparator for pembrolizumab in this indication as patients eligible for pembrolizumab would have already received all possible alternative treatments for metastatic melanoma which are known to impact survival (see sections 4.2.1 and 4.10.1). Dacarbazine was considered to be part of BSC (see sections 4.2.1 and 4.10.1).[11;12] A more detailed description of the systemic therapies considered as part of BSC is presented in section 5.5.5.

5.2.5 Discontinuation rules

Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity.

5.3 *Clinical parameters and variables*

5.3.1 Clinical data incorporated in the model

Data from the Phase II randomised-controlled KEYNOTE-002 trial was used to estimate the patients' baseline characteristics, the proportion of patients under the different health states, the proportion of patients experiencing AEs and the utilities used to populate the model. The licence for pembrolizumab is anticipated to cover the population of patients who are ipilimumab-treated. It was deemed inappropriate to pool data from the KEYNOTE-002 trial with that from the uncontrolled, phase I clinical trial KEYNOTE-001 (see Table 39 and Figure 21 of sections 4.9 for further details). Therefore, only KEYNOTE-002 data was finally incorporated into the economic model. This was deemed a conservative approach given the

lower treatment effect observed among patients treated with pembrolizumab in KEYNOTE-002.

KEYNOTE-002 studied a subset of patients eligible for pembrolizumab and who had been previously treated with ipilimumab. To assess the impact of this, a Cox-proportional hazards model was implemented. Since there were no ipilimumab-treated patients in the KEYNOTE-001 trial that had been treated with the 2 mg/kg dose, ipilimumab-treated patients from part B1 were compared to those ipilimumab-refractory patients from part B2 from KEYNOTE-001, given that all these patients were treated with the same dose and at a similar frequency (10mg/kg every 3 weeks; see Table 60).

Table 60: Cohorts compared in the assessment of the impact of refractoriness on outcomes[20;65]

Cohort from KEYNOTE-001	Ipi-refractory	Ipi-treated	Included
Part B1 10 mg/kg Q2W	0	16	No
Part B1 10 mg/kg Q3W	0	32	Yes
Part B2 10 mg/kg Q3W	84	0	Yes
Part B2 2 mg/kg Q3W	89	0	No

No significant difference was seen between the populations in terms of PFS (HR = 1.25; 95% CI: 0.70, 2.21; p = 0.45). This supports the results from the model applied to the wider population (see Figure 27). On the other hand, a significant difference was observed in terms of OS (HR = 2.40; 95% CI: 1.04, 5.51; p = 0.04), which demonstrated that a longer survival can be expected within the wider population compared to the population included within the KEYNOTE-002 trial (see Figure 28).

The cost-effectiveness model presented here used a combination of KEYNOTE-002 data for the first year (where there was a higher percentage of patients surviving and a potential underestimation of OS given the refractory nature of the patients), and external data, more in line with the population anticipated as part of the license. Consequently, the projected OS may somewhat underestimate the total OS of patients treated with pembrolizumab.

Figure 27: PFS comparison among the ipilimumab-treated patients (10mg dose) in KEYNOTE-001 (Part B1) and ipilimumab-refractory populations treated with pembrolizumab (10mg treatment arm) in KEYNOTE-002

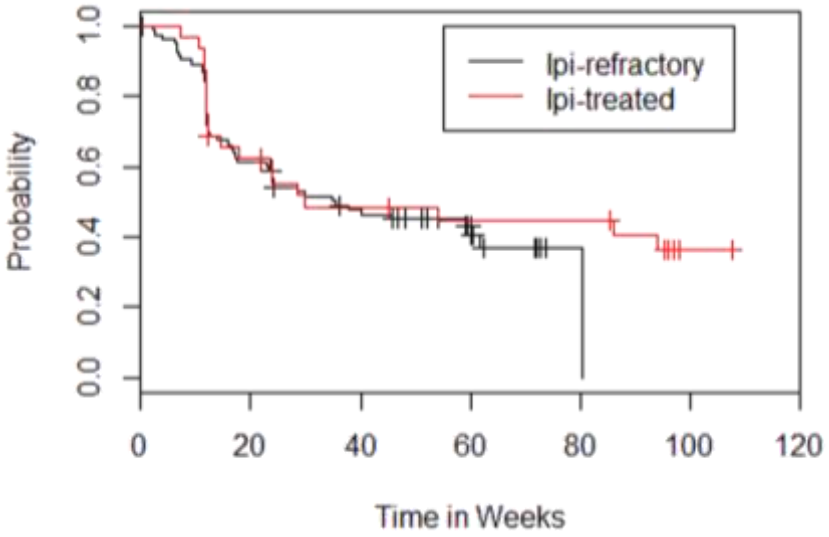
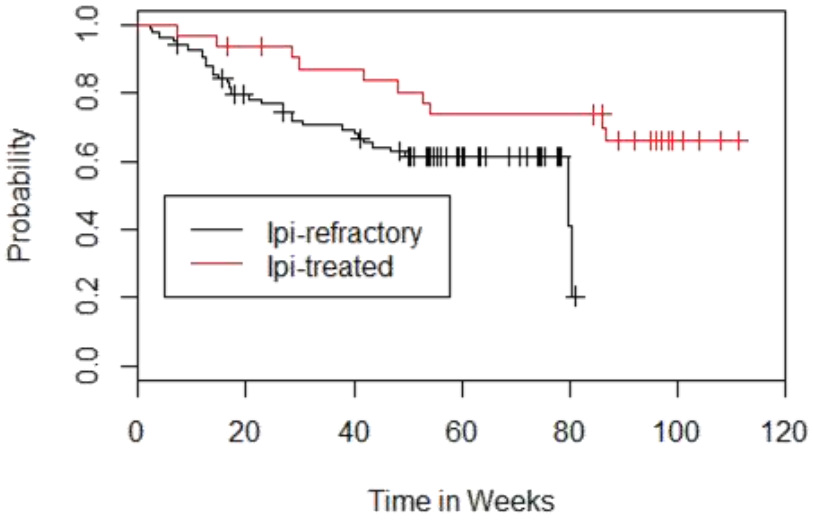


Figure 28: OS comparison among the ipilimumab-treated patients (10mg dose) in KEYNOTE-001 (Part B1) and ipilimumab-refractory populations treated with pembrolizumab (10mg treatment arm) in KEYNOTE-002



Due to the immaturity of the OS data in the KEYNOTE-002 trial, alternative methods to the standard parametric curve fit were required to extrapolate survival beyond the trial period. On the basis of the available data, pembrolizumab has been shown to achieve similar outcomes[20] as those reported by patients treated with ipilimumab in 2nd line.[80] This is expected given that pembrolizumab presents a similar mechanism of action to that of ipilimumab. Consequently, it should be expected that pembrolizumab will show a similar survival profile to ipilimumab in the long-term. This survival profile of ipilimumab showing a long-term benefit has been previously recognised by NICE.[1] 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. The study demonstrated a survival benefit plateauing at 3 years out of 10 years (the extent of the data available for analysis).[8] Making use of the previous information, pembrolizumab OS was extrapolated in the base case analysis. A summary of the clinical evidence used for pembrolizumab in the model and the corresponding strengths and weaknesses is presented in Appendix 15.

Survival associated with BSC was available from three key sources: the KEYNOTE-002 trial comparator arm, the MDX010-20 trial comparator arm (i.e. gp100) obtained from TA268[1] and the Korn dataset.[78] Within the model it was assumed that all chemotherapies had equal efficacy in terms of PFS and OS. This was in line with previous clinical advice received within the NICE submission for ipilimumab administered as 1st line,[2] where clinicians stated that dacarbazine would not be expected to be associated with increased survival compared to no treatment and that treatment was given primarily for symptom relief. This assumption was supported by the outcomes within these three datasets, which showed similar efficacy when differences in patient characteristics were adjusted for using the Korn algorithm.[78] These approaches are described in more detail in section 5.3.2 and 5.3.3 below.

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

PFS

Our modelling approach relies on data from KEYNOTE-002. As a consequence, the effect of 'tumour flare', which will lead to longer post-progression survival, has not been incorporated (see section 4.3.1 and Appendix 1).

OS

As previously mentioned (see section 4.3), patients included in the control arm of the KEYNOTE-002 trial who had documented disease progression following chemotherapy treatment were eligible to cross over to pembrolizumab. As the true survival benefit associated with pembrolizumab will be diluted due to crossover, conventional survival analysis will underestimate the survival benefit associated with pembrolizumab. Given the high level of crossover observed (86/179 patients; 48%), utilising the results of the ITT analysis for OS in the model was deemed inappropriate as the majority of patients in the chemotherapy arm of the trial received pembrolizumab.

Crossover in KEYNOTE-002 was typically related to disease progression and therefore non-random. Failure to account for non-random crossover was expected to overestimate OS in

the control arm even if there was an underlying clinical benefit from the investigational treatment. This was demonstrated by the fact that the median OS in the chemotherapy arm was 11.4 months, which was much higher than that previously observed among metastatic melanoma patients treated with chemotherapy (up to 9 months of median OS).[77-79] The NICE Decision Support Unit (DSU)[76] recommends the implementation of a variety of potentially appropriate crossover adjustment approaches when adjusting for this high level of crossover, taking into account the characteristics of the trial, the switching mechanism, the treatment effect, data availability and the adjustment method outputs. The methods recommended by the DSU include: the two-stage approach, the Inverse Probability of Censoring Weights (ICPW) method and the Rank Preserving Structural Failure Time (RPSFT) model. All these methods were implemented as part of this submission and their appropriateness assessed (see Table 61 and section 4.7).[76]

The first step to identify the relevant method to adjust for crossover among the RPSFT, two-stage and IPCW methods was to assess the treatment switching mechanism. Given that switching from the chemotherapy arm to the pembrolizumab arms in KEYNOTE-002 was determined by disease progression and the potentially relevant confounders were measured until this point, the two-stage approach appeared to be the most appropriate, since this method is valid when switching occurs after a specific disease-related time point (such as disease progression) and the relevant confounders are measured until this point in time.[76] The RPSFT method is based on the assumption that a 'common treatment effect' exists, while this assumption may not hold in practice since switchers to the pembrolizumab arms may experience a different treatment effect when they progress than that experienced by patients initially allocated to the pembrolizumab arms.

Based on the small sample size (compared to the observational datasets for which the IPCW was designed) and the high proportion of patients switching to pembrolizumab (48% of the total number of patients in the chemotherapy arm and 70% of those eligible for switching up to the point of the IA2; see Figure 29), it was uncertain whether the IPCW method could be a potentially valid, alternative method to adjust for crossover and would result in clinically valid results.[91]

Figure 29: Disposition of patients in the KEYNOTE 002 control group according to crossover

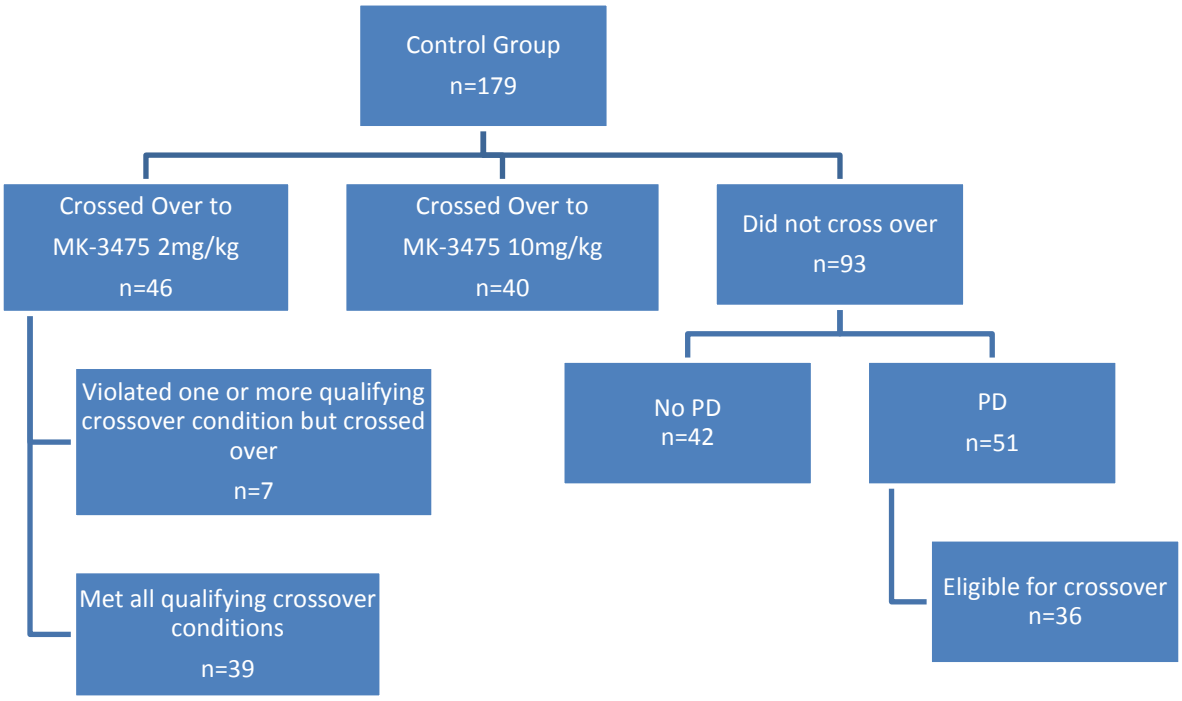


Table 61: Methodologies for crossover adjustment

Approach	Description	Comments on suitability
two-stage method	• Assumes a secondary baseline can be defined at which point patients are at risk of crossover (e.g. on progression) • Assumes no unmeasured confounders at the point of the secondary baseline • Assumes the RCT is appropriately randomised up until the point of disease progression	Suitable - as the potential to switch is determined by disease progression and potential confounders are measured until this point
IPCW	• Assumes no unmeasured confounders • Fails if there are any covariates which ensure (that is, the probability equals 1) that treatment switching will or will not occur • May become less stable and confidence intervals may become wide with small datasets (compared to the large observational datasets for which this method was defined) or with high levels of crossover	Potentially less suitable – uncertainty around the relatively small sample size within the trial (n = 359) and the relatively high proportion of patients switching over those eligible to switch
RPSFT	• Assumes treatment effect is equal for all patients no matter when the treatment is received • Assumes no differences between the treatment groups, apart from treatment allocated	Least suitable – as in reality treatment effect may be dependent upon progression status

IPCW: inverse probability of censoring weights; RPSFT: rank preserving structural failure time model; SNM: structural nested models.
Source: Derived from Latimer 2013[91]

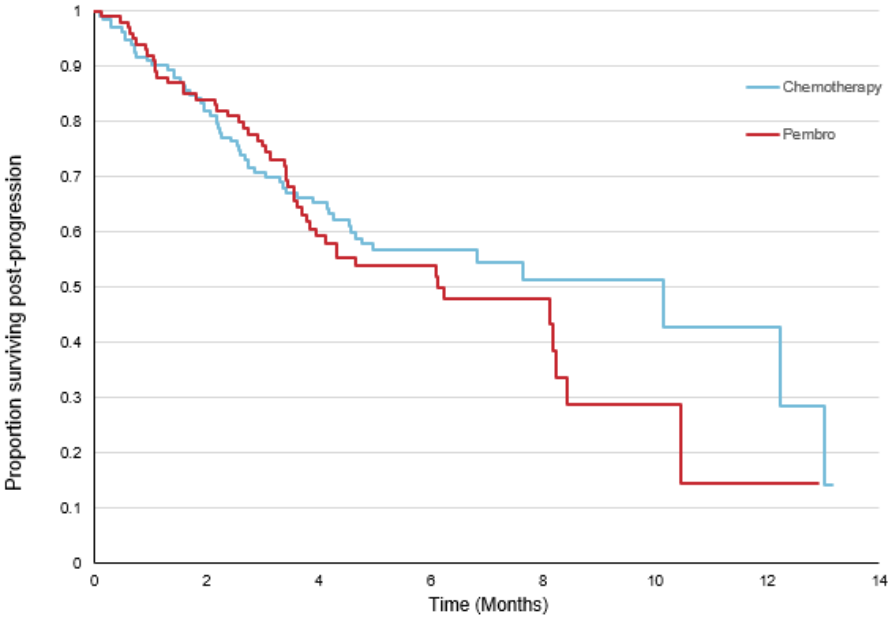
Several factors contributed to the final conclusion that the results of the RPSFT method are invalid. Firstly, the method seemed to fail to adjust for crossover, as demonstrated by the similarity between the curves obtained for the control arm before and after the RPSFT correction was applied (see Figure 10 and Figure 11 in section 4.7). The median RPSFT-adjusted OS was 11.1 months, while that historically associated with metastatic melanoma is up to 9 months, as previously mentioned.[77-79]

The results of the RPSFT method also imply that patients on pembrolizumab die more quickly post-progression than those on chemotherapy, while there is not a clinical rational for this effect. Figure 30 shows that the post-progression survival is similar for the two treatment arms (even when patients on the chemotherapy arm had access to alternative active treatment with pembrolizumab) for the initial period after progression, where results were most reliable and least confounded by crossover. This confirmed that patients on pembrolizumab did not die more quickly post progression than those on chemotherapy.

Figure 31 presents the post-progression survival curves for the pembrolizumab and chemotherapy arms of the KEYNOTE-002 trial. The chemotherapy arm is stratified according to whether patients crossed over to pembrolizumab. Patients receiving chemotherapy who did not crossover to pembrolizumab experienced a shorter survival than those receiving pembrolizumab or crossing over to pembrolizumab (see Figure 31).

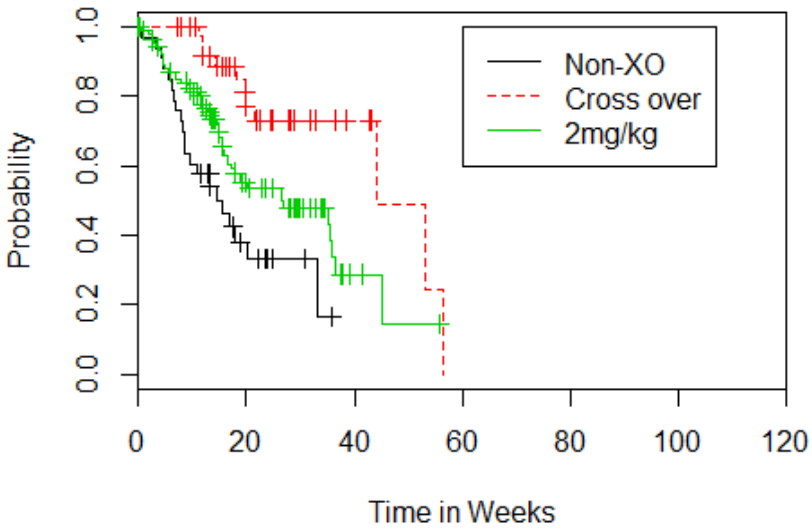
The adjusted results estimated by the RPSFT method were therefore considered to be implausible and not in line with either observed data or the results of the IPCW and two-stage methods (see below). Therefore, the RPSFT method has not been incorporated as part of the cost-effectiveness analysis.

Figure 30: Post-progression survival (after implementing RPSFT)



Time (months)	0	2	4	6	8	10	12	14
Chemotherapy	134	106	68	50	16	16	5	0
Pembrolizumab	105	83	46	36	25	6	1	0

Figure 31: Post-progression survival for the intervention group and the control group (the latter according to whether patients crossed over or not)

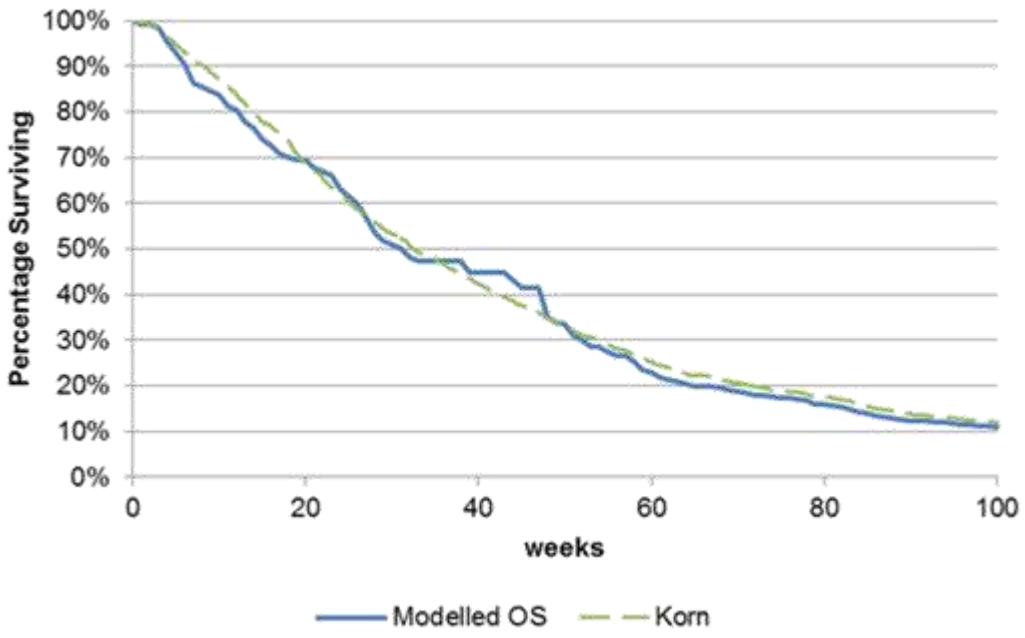


The two-stage crossover analysis[76;91] gave clinically valid results. Two models were run, one which adjusted for all potentially relevant covariates (including: ECOG, tumour size, LDH, BRAF status, melanoma stage and age; see Figure 13) and a second, simple model which only incorporated ECOG, as this was the only covariate which met the criteria for statistical significance (see Figure 12). Both models demonstrated a separation between the

pembrolizumab and the adjusted control arms, and led to similar results (see Table 25). Moreover, the median OS obtained from the two-stage adjustment was approximately 7.9 months (see Table 26). These results were in line with what would be expected from metastatic melanoma patients treated with chemotherapy based on available evidence.[77-79] Patients treated with chemotherapy presented therefore a median OS that was 3.5 months shorter than that for patients treated with pembrolizumab.

The adjusted OS obtained for the control group using the two-stage adjustment algorithm was validated using the Korn algorithm.[78] This algorithm was used to create an OS curve that reflected the characteristics of patients in the control arm of the KEYNOTE-002 trial. The generated curve served as a historical benchmark for the adjusted OS data generated with the two-stage algorithm for the control arm. As can be seen from Figure 32, the adjusted OS for the KEYNOTE-002 control arm, generated with the two-stage approach, presented a high degree of similarity with the predicted OS using the Korn algorithm.[78]

Figure 32: Comparison of the adjusted OS using the two-stage approach vs. the Korn data[78] (adjusted to reflect the characteristics of KEYNOTE 002 patients)



IPCW was originally designed for use with large observational datasets and was therefore expected to be less appropriate for the crossover adjustment of the KEYNOTE-002 trial. Missing data for the analysis was dealt with by applying the last observation carried forward approach. The hazard ratio produced from the IPCW crossover analysis was 0.677 (95% CI: 0.478, 0.959; se = 0.178). These results were consistent with those from the two-stage method (see Table 25) indicating that despite the limited sample size available from the trial,

the high proportion of patients crossing over and the missing data, the IPCW method appears plausible.

After applying these alternative crossover adjustment methods, the two-stage crossover approach was deemed to be the most appropriate, as described above. Therefore, this approach was used in the base case analysis. The two-stage full covariate adjustment model was used as this was the more conservative of the two models applied.

5.3.3 Extrapolation

Standard parametric curve fitting of the PFS and OS data derived from the KEYNOTE-002 trial was initially considered for the extrapolation of the data in the long term. The survival curve fitting was carried out in line with the NICE DSU guidelines,[92] and all standard parametric models (exponential, Weibull, Gompertz, log-logistic and log-normal) were considered and compared.[91] 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).

PFS

In KEYNOTE-002 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 chemotherapy PFS data in order to extrapolate beyond the trial period (see Appendix 16). Therefore, a two-part curve fit was applied to the PFS data to account for this: KM curves 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 ($p = 0.969$) does not rule out using the proportional hazard ratio assumption. Additionally, the proportional hazard assumption could not be rejected based on a visual inspection of the two-residual plot (see Figure 33). The confidence bands were considerably wide and a potential turning point around week 20 could not be confirmed. Therefore, a pooled model was used for all the arms included in the KEYNOTE-002 clinical trial for the projection of the PFS using a 2-part extrapolation.

Figure 33: Two-residual plot

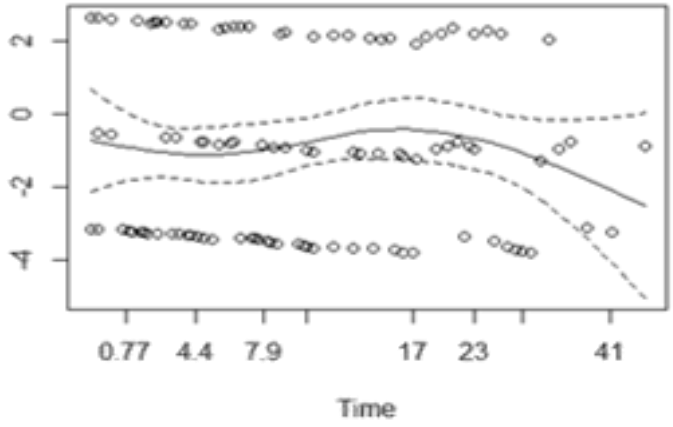


Table 62 reports the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) for the second part of the two-part curve fit for PFS for pembrolizumab and BSC. According to both the AIC and the BIC criteria, Gompertz was the best fit to the PFS data for pembrolizumab and Log-logistic the best fit to the BSC PFS data, independently of the criteria used.

Table 62: AIC and BIC for PFS curve fit for week 13+

	Model for pembrolizumab and BSC for week 13+ (to use in the 2-part extrapolation)	
Model	**AIC**	**BIC**
Exponential	1045	1044
Weibull	1044	1047
LogNormal	1052	1055
LogLogistic	1047	1050
Gompertz	**1029**	**1044**

AIC; Akaike information criterion. BIC; Bayesian information criterion

The curve fits for pembrolizumab and BSC are presented in Figure 34 and Figure 35, respectively. Following visual inspection of the curves, Gompertz was selected to be the best fitting curve for pembrolizumab due to its AIC and BIC values and the curve being clinically as expected. As previously mentioned (see section 5.3.2), using PFS to represent disease status within the model may underestimate pre-progression survival and overestimate post-progression survival; therefore, it may not fully capture the impact of treatment.

Figure 34: PFS in the pembrolizumab arm

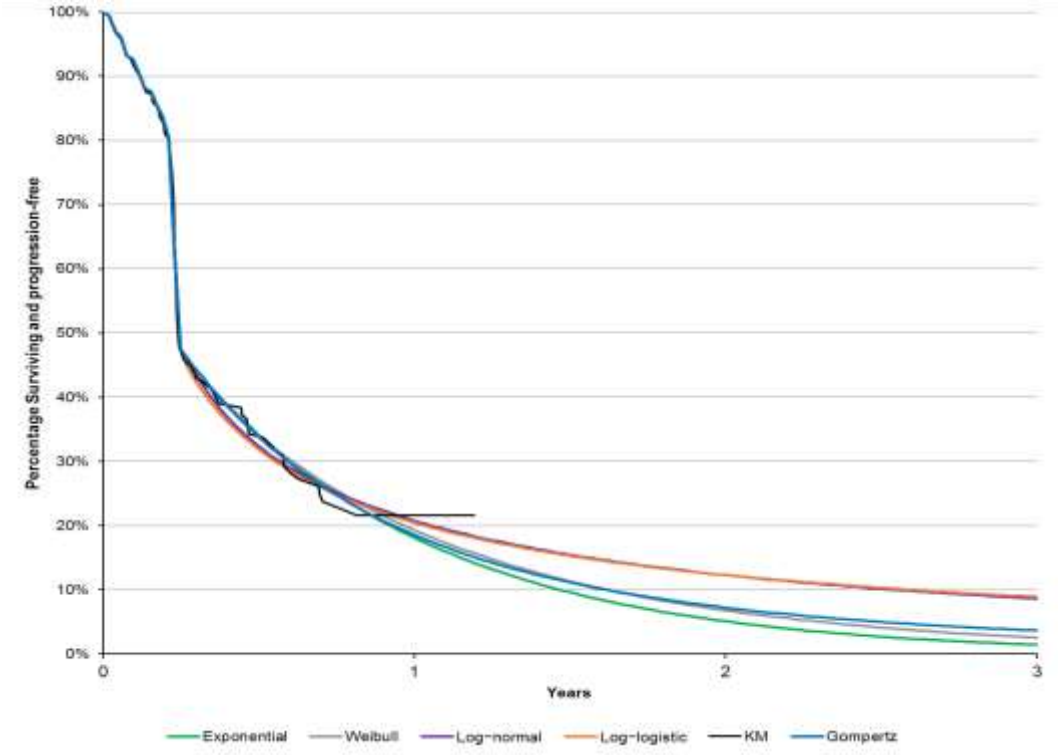
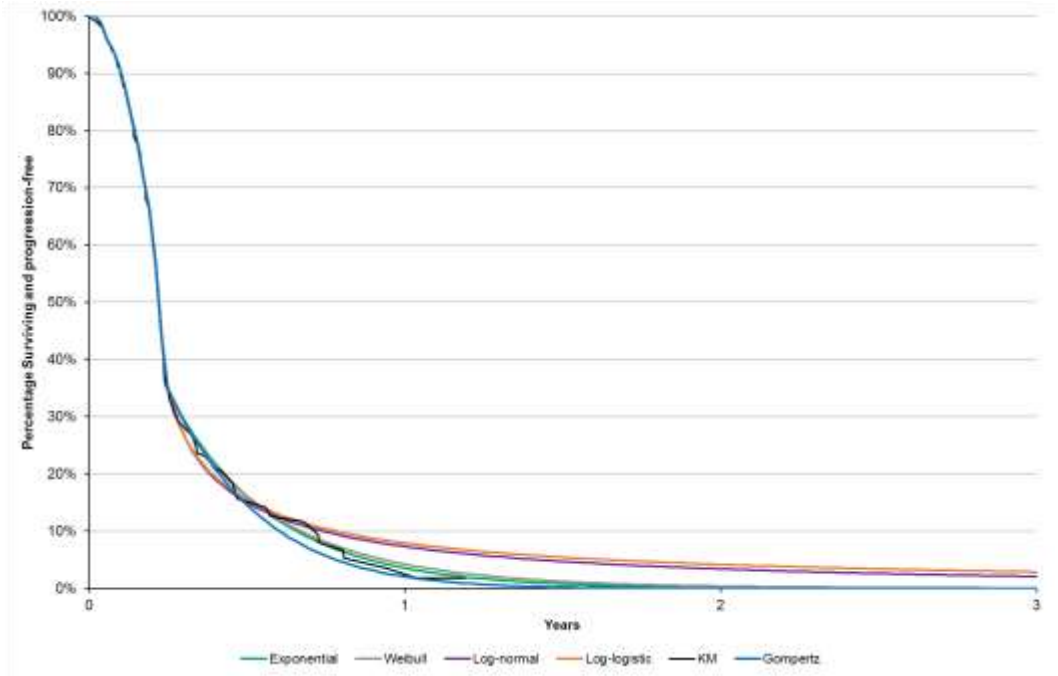


Figure 35: PFS in the chemotherapy arm



OS

The OS data in the KEYNOTE-002 trial was immature (see section 4.7). Moreover, the standard parametric curve fitting resulted in survival estimates that were mostly not clinically

plausible, as long-term survival for pembrolizumab was projected below what would be expected with standard chemotherapies/no treatment (see Appendix 16). This was consistent with the findings from the previous submissions for ipilimumab, both administered as 1st and a 2nd line treatment. 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 in the long term for immunotherapies.[1;2] Therefore, it was deemed inappropriate to use a standard parametric curve fit based only upon within trial data.

Alternative methods to the standard parametric curve fit were considered to extrapolate survival beyond the trial period. A summary of the options considered is presented in Table 63 and a more detailed discussion is presented below.

Table 63: Summary of extrapolation options for pembrolizumab and comparator arm

Pembrolizumab	Comparator
Trial data + ipilimumab extrapolation from Schadendorf 2015 (relative rate of survival) PFS KM data from the KEYNOTE-002 trial is used for the first 12 weeks, and a parametric curve (best fit: Gompertz distribution) is fit to the KEYNOTE-002 pembrolizumab arm from week 13. For OS, KM data from the KEYNOTE-002 trial is used for 1 year (number at risk = 22/ 180); then, a curve made of the ipilimumab survival curve (as published in Schadendorf 2015[8]) is used until year 10; registry data is used thereafter,[77] using conditional probabilities, assuming the same percentage of patients die. As the registry data[77] only reports melanoma specific mortality, background survival is applied on top of this.[93] **Summary of the data used for OS:** • 0 to 1 year – KEYNOTE-002 trial data • 1 year to 10 years – Schadendorf data (previously treated) • 10 years + - Balch 2001 registry data + general population mortality	**Chemotherapy from KEYNOTE-002, two-part curve fit** PFS KM data from the KEYNOTE-002 trial is used for the first 12 weeks. A parametric curve (best fit: Gompertz distribution) is fit to the chemotherapy arm of the KEYNOTE-002 trial from week 13. For OS, survival is modelled based upon the curve fit selected for pembrolizumab adjusted for crossover using the two-stage method. No external data is used outside of the trial.
Trial data + ipilimumab extrapolation from MDX010-020 (using relative rate of survival) PFS KM data from the KEYNOTE-002 trial is used for the first 12 weeks, and a parametric curve (Gompertz distribution) is fit to the KEYNOTE-002 pembrolizumab arm from week 13. For OS, the KM data from the trial is used for 1 year (number at risk = 22/ 180); then, the ipilimumab survival curve, as published in TA268[1] (i.e. MDX010-20 trial KM + curve fit + Balch 2001 registry data) is appended, using conditional probabilities, assuming the same percentage of patients die. As the registry data[77] only reports melanoma specific mortality, background survival is applied on top of this.[93] **Summary of the data used for OS:** • 0 to 1 year – KEYNOTE-002 trial data • 1 year to 1.5 years – MDX010-020 KM data • 1.5-5 years – curve fit to MDX010-020 data • 5 years + - Balch 2001 registry data + general population mortality	**gp100 from MDX010-020 trial as a proxy for BSC** For PFS, the gp100 PFS curve published in TA268[1] is used. For OS, the gp100 survival curve published in TA268[1] (i.e. MDX010-20 trial KM + curve fit + registry data) is considered, using conditional probabilities and assuming the same percentage of patients die. Curves have been adjusted for differences in patient characteristics across trials using the Korn algorithm as per TA319.[2] **Summary of the data used for OS:** • 0 to 1 year – MDX010-020 gp100 KM data • 1-5 years – curve fit to MDX010-020 data • 5 years + - Balch 2001 registry data + general population mortality • Korn model to adjust for differences in patient characteristics
HR using KEYNOTE-002 on external data PFS KM data from the KEYNOTE-002 trial is used for the first 12 weeks, and a parametric curve (Gompertz distribution) is fit to the KEYNOTE-002 pembrolizumab arm from week	**Korn dataset (OS only)** For OS, the published Korn survival curve is considered. Curves have been adjusted for differences in patient

Pembrolizumab	Comparator
13. For OS, the hazard ratio between the pembrolizumab and the chemotherapy arms from the two-stage crossover analysis is applied to a selected external dataset (gp100 from MDX010-020).	characteristics across trials using the Korn algorithm as per TA319.[2] **Summary of the data used for OS:** • 0 to 5 years – Korn KM data • 5 years + - Balch 2001 registry data + general population mortality Korn model to adjust for differences in patient characteristics
Trial data + ipilimumab extrapolation from Schadendorf 2015 – Treatment naïve cohort (relative rate of survival) PFS KM data from the KEYNOTE-002 trial is used for the first 12 weeks, and a parametric curve (best fit: Gompertz distribution) is fit to the KEYNOTE-002 pembrolizumab arm from week 13. For OS, KM data from the KEYNOTE-002 trial is used for 1 year (number at risk = 22/ 180); then, a curve made of the ipilimumab survival curve (as published in Schadendorf 2015 for treatment-naïve patients[8]) is used until year 10; registry data is used thereafter,[77] using conditional probabilities, assuming the same percentage of patients die. As the registry data[77] only reports melanoma specific mortality, background survival is applied on top of this.[93] **Summary of the data used for OS:** • 0 to 1 year – KEYNOTE-002trial data • 1 year to 10 years – Schadendorf data (treatment-naïve patients) • 10 years + - Balch 2001 registry data + general population mortality This is based upon clinical advice that long-term survival with pembrolizumab would be expected to be at least as good or better than that seen with ipilimumab.	

Approaches followed to extrapolate pembrolizumab in the long-term

1) Using the ipilimumab long-term survival curve from Schadendorf (2015)[8] (assuming the same relative rates of survival)

Since pembrolizumab is an immunotherapy like ipilimumab, it is expected that it would have a similar survival profile in the long-term.[8] This is in line with both clinical opinion received by MSD and the results currently available from KEYNOTE-002[20] and KEYNOTE-006 trials,[14] as described below.

Although patients included in KEYNOTE-002 had a poorer prognosis than those in MDX010-020 (particularly in terms of performance status and severity of metastasis; see Table 64), median PFS, median OS and PFS at 6 months were similar across both groups of patients, with a trend in favour of the patients treated with pembrolizumab (see Table 65). PFS has been found to be a robust surrogate for OS in dacarbazine-controlled trials in metastatic melanoma and this association is expected to hold for other treatments.[94] Therefore, the PFS results observed for pembrolizumab in the short term are expected to be observed for OS in the longer term.

Table 64: Comparison of baseline characteristics of patients included in KEYNOTE 002 and MDX010-020

	Pembrolizumab			***Ipilimumab***		
	KEYNOTE-002[20]			**MDX010-020[80]**		
	2mg	10mg	Chemotherapy	Ipi+GP100	Ipi	GP100
N	180	181	179	403	137	136
Male (%)	57.80%	60.20%	63.70%	61.30%	50.10%	53.70%
Age mean	59.50	60.10	60.50	55.60	56.80	57.40
ECOG 0 (%)	54.40%	54.10%	55.30%	57.60%	52.60%	51.50%
ECOG 1 (%)	44.40%	45.90%	44.70%	41.20%	46.70%	44.90%
M1c stage at entry (%)	82.20%	82.90%	82.10%	70.70%	73%	72.10%
Elevated LDH (%)	42.80%	40.30%	38%	37%	38.70%	38.20%

Table 65: Comparison of results from KEYNOTE 002 and MDX010-020

	Pembrolizumab KEYNOT-002[20]2			***Ipilimumab MDX010-020[80]***		
	2mg	10mg	Chemo	Ipi+GP100	Ipi	GP100
Median OS	11.4	12.5	11.6	10	10.1	6.4
Median PFS	2.9	2.9	2.7	2.76	2.86	2.76
PFS rate at 6 months	34.30%	37.70%	15.60%	_ 17%	_ 20%	_ 5%

Additionally, the results of the KEYNOTE-006 trial demonstrated that pembrolizumab met its two primary endpoints of significant improvement in PFS and OS (see section 4.7).[80] On this basis, the expectation is that pembrolizumab will deliver a greater proportion of patients surviving in the longer term compared to ipilimumab.

Under this modelled extrapolation scenario, the KM data from the KEYNOTE-002 trial until 1 year (number at risk = 22/ 180) was used. A curve consisting of the long-term ipilimumab survival data[8] was appended until year 10 (considering only the data derived from patients who had been previously treated). Thereafter, registry data[77] was used (see Appendix 17 for the published curve fits).[2] Based on the proportion of patients in these stages in the KEYNOTE-002 trial, the stage IIIC and the stage IV data from the registry data were combined, following the approach previously implemented in TA319. [2] The registry data only reported melanoma specific mortality; therefore, background survival was applied in addition.[93] 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 patients previously treated. Clinicians indicate they believe that a larger proportion of patients can be expected to survive in the longer term with pembrolizumab.

Based on clinical input, we have modelled the treatment naïve cohort curve from Schadendorf 2015[8] as a sensitivity analysis given that it shows a greater proportion of patients surviving than for the previously-treated population, thus modelling their expectations of pembrolizumab.

2) **Extrapolation of pembrolizumab using the ipilimumab survival curve from TA268 (assuming the same relative rates of survival)**

The published survival curves from TA268[1] using data from the MDX010-20 clinical trial were also used as an alternative option for extrapolation. In this extrapolation approach the KM data from the KEYNOTE-002 trial until 1 year (number at risk = 22/ 180) was used; then, the ipilimumab survival curve was appended as published in TA268[1] (i.e. by using KM data from MDX010-020 for 0 to 18 months, then the curve fit from 18 months to 5 years, followed by registry data[77] from year 5 onwards) using conditional survival probabilities, as noted above. As the registry data[77] only reported melanoma specific mortality, background survival was applied on top of this.[93]

3) **HR using KEYNOTE 002 crossover analysis applied to external data**

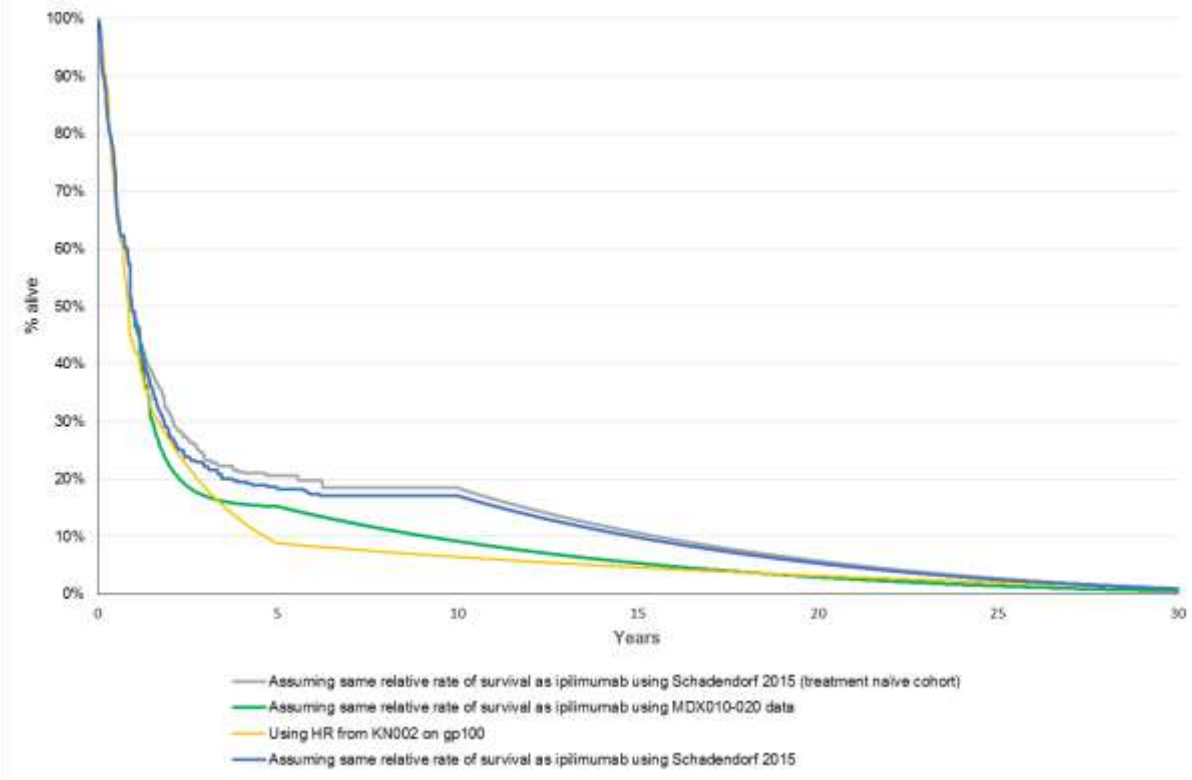
The HR between the pembrolizumab and chemotherapy arms from the two-stage crossover analysis was applied to two long-term external datasets in an alternative extrapolation scenario to represent the expected chemotherapy outcomes reflected as BSC (using either gp100[1] or the Korn dataset[78]). External comparator datasets have been adjusted to the patient characteristics in the KEYNOTE-002 trial using the Korn algorithm.[78] This is applied by calculating a HR from the patient characteristics from the external trial and the coefficients published in the study (see Table 66).[78]

Table 66: Korn model for adapting MDX010-20[1]

	Coefficient	MDX010-20
Male	0.248	61%
ECOG1	0.436	41%
ECOG2+	0.948	1%
M1b + M1c	0.421	89%
Brain Metastases	0.304	12%
Hazard Ratio		0.9821

Figure 36 compares the overall survival curves for all the extrapolation approaches implemented to estimate the OS of pembrolizumab.

Figure 36: Comparison of all OS extrapolation approaches



Approaches followed to extrapolate BSC in the long-term

The model allowed for alternative sources of efficacy to be used to estimate BSC survival, including:

1) **Using the chemotherapy comparator arm from KEYNOTE-002 trial**

As mentioned above, a two-part curve fit was applied to the chemotherapy PFS data by using the PFS KM curve until week 13 and thereafter a parametric curve fit (Gompertz being the best fit), so that the protocol-driven drop happening between weeks 12 and 13 could be accounted for. To extrapolate the OS associated with BSC, the HR obtained from the two-stage crossover adjustment was applied to the pembrolizumab projected data (see Table 25). This was the base case included in the model.

2) **Using gp100 from the NICE submission for ipilimumab in 2nd line (TA268)[1]**

The MDX010-20 trial comparator arm from the ipilimumab 2nd line submission (i.e. gp100)[1] was also used as an alternative, potential proxy for the BSC arm in the cost-effectiveness analysis.

The KM curves for OS and PFS from the gp100 arm assessed in the MDX010-020 trial were digitised. The PFS curve was extrapolated using the parameters published in TA268.[1] The

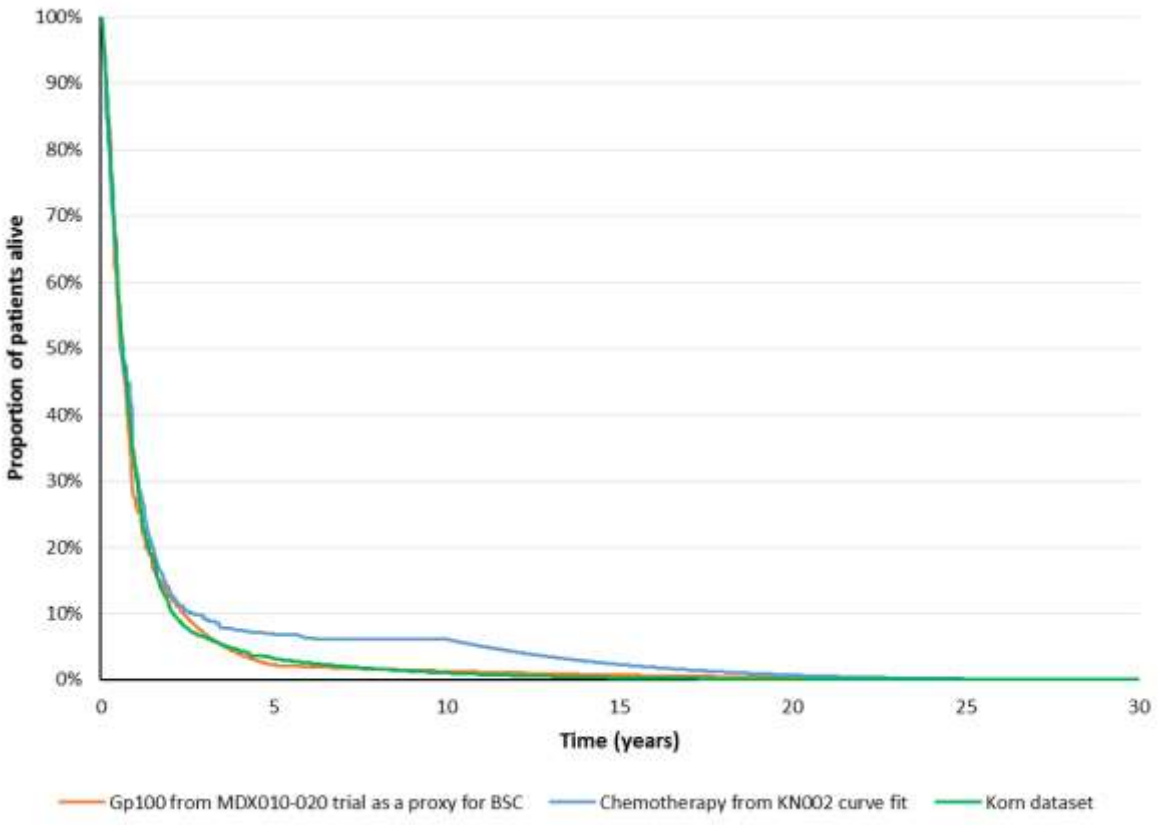
OS curve was applied in the same way as the three-part curve published in TA268,[1] that is, by fitting an exponential curve using the published parameters and then registry data after 5 years.[77] The gp100 curves were adapted using the Korn algorithm to adjust for the difference in patient characteristics between the two trials. [78] Using gp100 as a proxy for BSC presented the advantage that the MDX010-020 trial was also conducted in patients who had received previous treatment but a longer follow-up was available from the trial data (up to 5 years); moreover, the use of this methodology for extrapolation has been previously accepted by NICE.[1]

This approach was considered to be conservative compared to using the Korn data, the other alternative external source of data available (see Figure 37).

3) **Using the Korn data set (for OS only)** [78]

The Korn dataset represents the natural survival of patients with metastatic melanoma treated with chemotherapy and was used as an alternative representation of the BSC OS data. This approach assumed that patients who had previously received ipilimumab would present a similar survival to that of historical patients who had not received this treatment. This dataset contained the greatest length of follow-up from the largest number of patients (n=2100; length of follow-up = 5 years).

Figure 37: Comparison of possible comparator curves



When the survival curves obtained from the gp100, Korn and chemotherapy trial data were compared, all three curves showed a very similar profile for the first year (see **Error! eference source not found.**). This validates both the assumptions made in terms of equal efficacy for chemotherapy regimens and the validity of the estimated hazard ratio for chemotherapy compared to pembrolizumab derived using the two-stage crossover method.

In the long term projection of BSC using KEYNOTE-002 relies on the assumption of proportional hazards for chemotherapy compared to immunotherapy. Long-term survival with chemotherapy has never been attributed to chemotherapy and is instead thought to be down to the body's natural immune system. Immunotherapy works by activating the immune system, thereby simulating the same type of response but in a greater proportion of patients. In the short-term the assumption of proportional hazards was confirmed as comparison of outcomes with gp100 and chemotherapy using a proportional hazards approach indicated nearly identical survival profiles. It is likely that in the long-term the assumption of proportional hazards overestimated the benefits of chemotherapy; therefore, this approach was considered to be conservative. Long term data for gp100 and the Korn curves showed a very similar efficacy profile. The curve from the KEYNOTE-002 trial data was, however, used in the model base case as the more conservative approach (see Figure 37).

5.3.4 Input from clinical experts

Three leading melanoma clinical experts were consulted to discuss the validity of the approach used to modelling PFS and OS, and the clinical plausibility of the projections from the clinical trial data, in addition to the results obtained to adjust for crossover. No questionnaires, individual interviews or Delphi techniques were needed since no estimation of specific clinical parameters was required (given that data and assumptions used were derived from available clinical evidence). There was general agreement that it was reasonable to assume the following:

- Similar survival to that observed from the long-term follow-up of patients treated with ipilimumab in second or subsequent treatment lines.[8] The actual expectation is that pembrolizumab will result in a higher proportion of patients surviving over time compared to ipilimumab, as demonstrated by the preliminary results of the KEYNOTE-006 trial. The study was stopped early since it met its two primary endpoints of PFS and OS. Given the lack of long term data for pembrolizumab it was deemed appropriate to remain conservative in the base case and assume similar outcomes to those of ipilimumab. A best-case scenario was considered in the sensitivity analysis using the ipilimumab long-term data from the treatment-naïve population.

- The projections obtained appeared clinically plausible.

- The clinicians accepted that there was a need to adjust for crossover. They were unable to recommend a method based on lack of knowledge in the area but expected to see a survival benefit demonstrated for pembrolizumab once the adjustment was undertaken.

The selection of the clinicians was based upon availability given the short time frame between developing the model and the submission deadline. Each clinician volunteered for no payment to review the proposed approach and provide validation. Although not a random selection, the clinicians worked in three different widely separated centres in England. They all currently treat patients with metastatic melanoma and have experience of using ipilimumab in practice and pembrolizumab either as an investigator for a clinical trial or through EAMS.

5.4 Measurement and valuation of health effects

The burden of metastatic melanoma from the patient perspective has been evaluated in several clinical trials.[47] The immediate period following diagnosis was often associated with high levels of HRQL 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.[47] The most common patient-reported, HRQL impairments are elevated pain and fatigue.[95]

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.[96]

HRQL is often similar to the expected quality of life of members of the general population until the months immediately prior to end of life.[97-100]

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.[47;98-100] 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.[98-100]

5.4.1 Health-related quality-of-life data from clinical trials

The only trial assessing pembrolizumab and evaluating HRQoL was the KEYNOTE-002 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 II study (KEYNOTE-002), changes from baseline in the HRQoL for ipilimumab refractory patients treated with pembrolizumab were compared to those from patients treated with chemotherapy. 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 chemotherapy/pre-crossover; discontinuation/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).[101] Evaluation of HRQoL using EQ-5D directly from patients is consistent with NICE reference case and is used in the cost-effectiveness model.[102]

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.[101] EQ-5D data have been derived from the KEYNOTE-002 clinical trial; therefore, there was no need to map the EORTC QLQ-C30 values collected in the KEYNOTE-002 to EQ-5D.

The PRO analyses are based on the FAS population. Results for both EQ-5D and EORTC QLQ-C30 questionnaires reported below were based on the second interim analysis of KEYNOTE-002 (data cutoff date: 12 May 2014). Results are presented across this section for pembrolizumab 2mg/kg Q3W (anticipated licenced dose; and dosage relevant to this submission) versus the comparator of interest (investigator choice chemotherapy). More details relative to the statistical analysis performed on EQ-5D with the corresponding results are provided in Appendix 20.

EQ5D:

The proportion of missing reported EQ-5D data is lower than 10%. Therefore complete case analyses were used to assess HRQL.

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-002 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique (see Appendix 20).[103]

A diagnostic analysis conducted to compare baseline EQ-5D utility scores, collected at the 1st visit (treatment cycle 1), showed that there was no significant difference in baseline utilities across the three 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 HRQL 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.[100] Therefore, alternative approaches to

implementing HRQL were used in ipilimumab 1st line (TA319)[2] NICE submission using time to death utility values. This approach was accepted as the most preferable in ipilimumab 1st line submission (TA319).[2]

In the base case scenario, the values used for the time to death utilities in the model were the pooled values from the 2mg/kg pembrolizumab arm and the chemotherapy arm, as there was no significant difference in quality of life between the two arms.

In line with the methodology accepted in TA319 [2] 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 [2] (see Appendix 20). Fewer categories were used due to the smaller sample size available within the trial. 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.

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 180 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 180 or more days to death, patients with censored death date of 180 days or longer were also included since their EQ-5D data related to a survival of at least 180 days, independently of when the death date was censored.

HRQL has been age-adjusted using the values from Kind et al;[104] as the average age of patients increases (up to the 75+ age band) a utility decrement of 0.0038 (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.

- <u>Progression based utilities</u>

Utility values were also calculated based upon the trial data for both pre-progression and post-progression for both treatment arms (Table 67):

- 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 two different assessment approaches: IRO (by independent review committee and oncologist review) and INV (by investigator review). The IRO results are reported by both an independent review committee and an oncologist and were therefore deemed more conservative (Table 67). The utility values obtained from the INV approach are presented in the EQ-5D report that is integrated in Appendix 20.

Based on the second interim analysis of the KEYNOTE-002 trial, a comparison analysis based on baseline utilities showed that there was no statistical significant difference across treatment groups so the utilities between the chemotherapy and the pembrolizumab 2mg/kg were pooled together (Table 67).

Table 67: EQ-5D health utility score analysis based on progression from KEYNOTE-002 trial (by IRO assessment)

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	164	436	0.75	0.27	(0.73, 0.78)	147	297	0.73	0.24	(0.71, 0.76)	311	733	0.74	0.25	(0.73, 0.76)
Progressive	85	127	0.69	0.31	(0.63, 0.74)	102	139	0.68	0.27	(0.63, 0.72)	187	266	0.68	0.29	(0.65, 0.72)

† 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-002 trial were used in sensitivity analysis (i.e. 0.74 for those in the pre-progression health state and 0.68 for those who have progressed).

EORTC QLQ-C30:

Full EORTC QLQ-C30 results are reported in Appendix 27.

5.4.2 Mapping

Not applicable as HRQoL was derived from the KEYNOTE-002 EQ-5D data.

Utilities were evaluated using EQ-5D directly from patients from the KEYNOTE-002 trial, which is consistent with the NICE reference case.

Health-related quality-of-life studies

5.4.3 Systematic searches for relevant HRQL data

The relevant HRQL 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 19 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 HRQL (in terms of utilities) associated with advanced melanoma.

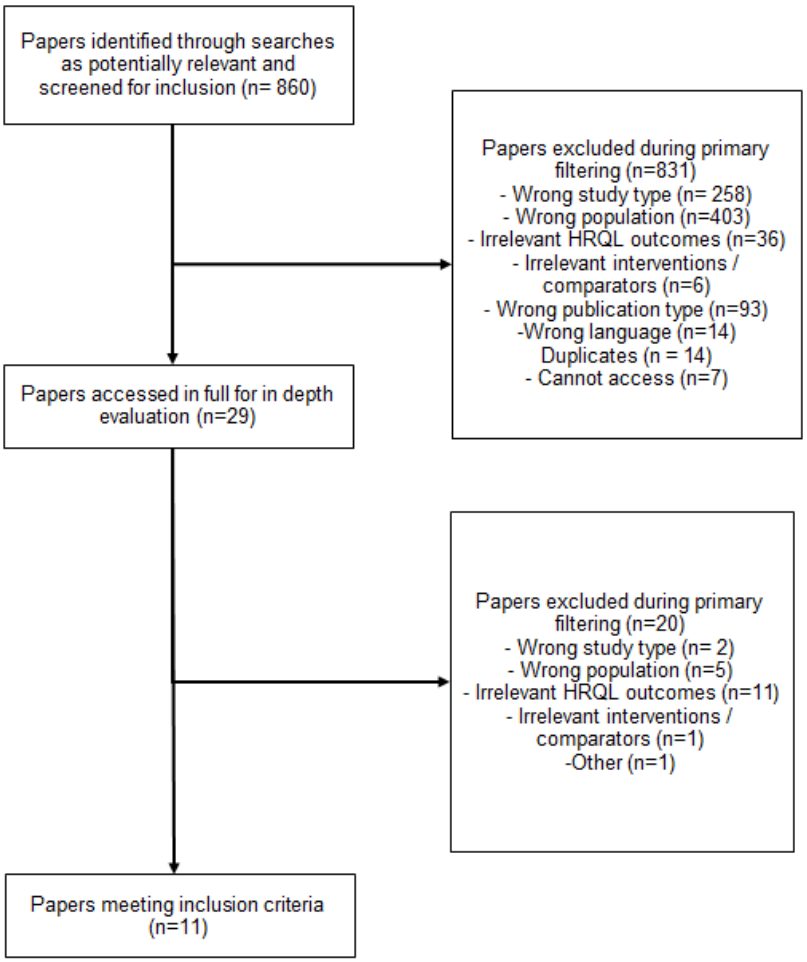
A comprehensive literature search relative to this research questions was carried out using the different databases presented in section 5.1: MEDLINE and MEDLINE In-process (using Ovid platform); EconLit; EMBASE; The Cochrane Library, including the following NHS EED and HTA database.

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 19 provides details relative the eligibility criteria for the HRQL 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 HRQL and utilities search (Figure 38).

Figure 38: PRISMA Diagram: HRQL and Utility studies



Key: *HRQL, Health-related quality of life.*

As no study assessing patients previously treated 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 68.

5.4.4 Provide details of the studies in which HRQL was measured

Table 68: Characteristics of the HRQL and utility studies identified

Authors	Date	Population	Setting	Method of derivation	Utilities included	SD/SE/range or CI's
Askew et al.[97]	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

Authors	Date	Population	Setting	Method of derivation	Utilities included	SD/SE/range or CI's
Barzey et al.[105]	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.[106]	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.[98]	2012	Advanced melanoma	UK	EORTC QLQ-C30 mapped to the EORTC-8D	Pre progression: 0.80 Post progression: 0.76	

Authors	Date	Population	Setting	Method of derivation	Utilities included	SD/SE/range or CI's
Beusterien et al.[96]	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 All (UK and Australia): Partial Disease: 0.88 Stable disease: 0.80 Progressive disease 0.52 Best supportive care (BSC): 0.52	SE: UK: Partial response: 0.02 Stable disease: 0.02 Progressive disease: 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.[99]	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

Authors	Date	Population	Setting	Method of derivation	Utilities included	SD/SE/range or CI's
Hatswell et al.[100]	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 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.[107]	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

Authors	Date	Population	Setting	Method of derivation	Utilities included	SD/SE/range or CI's
King et al.[108]	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 Stage IV median:0.500	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 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.[109]	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.[110]	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 68 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.

The utilities coming from the KEYNOTE-002 trial are similar to those found in other trial based studies. Ipilimumab utilities reported in the previously treated NICE STA submission,[1] derived using the EORTC-8D, are slightly higher than the ones reported in the KEYNOTE-002 trial for both pre-progression and post-progression (Table 69).

Table 69: Comparison of utilities reported used in both ipilimumab previously treated and KEYNOTE-002 economic models

	KEYNOTE-002 - Pooled (Chemotherapy and 2mg/kg) (Weighted Average) (IRO)(Appendix 20)	2nd line ipilimumab NICE submission (TA268)[1]
Pre-progression	0.74	0.80
Post-progression	0.68	0.76

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-002, 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),[2] Askew et al[97] found an average utility of 0.86 for stage IV patients and Dixon et al[99] found an average utility of 0.77 at 3 months and 0.87 at 48 months of follow-up.

Adverse reactions

5.4.6 Describe how adverse reactions affect HRQL

Immunotherapy checkpoint inhibitors, such as ipilimumab and pembrolizumab, are associated with a broad range of adverse events, particularly immune-related, that can affect the HRQoL of patients, and that can be serious or fatal. Immune-related adverse events have been reported to be less commonly associated with use of pembrolizumab compared to other immunotherapies such as ipilimumab.[111]

Section 4.12.2 reports the AEOSIs associated with use of pembrolizumab in the 2mg/kg treatment arm versus chemotherapy in KEYNOTE-002. These results show that overall 16.3% of subjects on the 2mg/kg Q3W pembrolizumab treatment arm were reported to have any AEOSIs at the time of this analysis. However, most of the cases reported are grade 1-2 severity, with 5 subjects (2.8%) on the 2mg/kg Q3W experiencing grade 3-4 AEOSIs.

Unfortunately few questionnaires were available in order to be able to undertake direct analysis of the impact of specific AEs on HRQoL directly from the trial data. Published literature on the impacts of specific AEs has therefore been used in preference within the cost-effectiveness modelling.

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 71 reports the EQ-5D utilities from KEYNOTE-002 following assessment by IRO. Analysis of utilities of grade 3-5 adverse events for patients in progression-free state is presented in Table 70, when patients experience a grade 3-5 AE, and when they do not.

Table 70: EQ-5D Health Utility Scores in progression-free state: with and without Grade 3-5 AEs (progression by IRO assessment)

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
During Grade3-5 AEs	38	79	0.53	0.33	(0.45, 0.60)	38	73	0.61	0.30	(0.54, 0.68)	76	152	0.57	0.32	(0.52, 0.62)
Without Grade3-5 AEs	141	378	0.79	0.23	(0.76, 0.81)	126	238	0.75	0.22	(0.72, 0.78)	267	616	0.77	0.23	(0.76, 0.79)

† 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

Health-related quality-of-life data used in cost-effectiveness analysis

5.4.7 Definition of the health states in terms of HRQL in the cost-effectiveness analysis.

HRQL 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 HRQL is assumed to be constant over time in the cost-effectiveness analysis

A constant value for HRQL is associated to each health state and a utility decrement of 0.0038 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 HRQL 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. HRQL 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 HRQL in the final months of life of advanced melanoma patients and this approach was previously accepted in the ipilimumab 1L submission (TA319).[2]

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 71.

Table 71: Summary of utility values for cost-effectiveness analysis (IRO)

Time to Overall Survival (days)	2 mg		Chemotherapy		Total		Reference in submission (section and page number)	Justification
	Mean	95% CI	Mean	95% CI	Mean	95% CI		
≥180*	0.78	(0.75, 0.81)	0.75	(0.72, 0.79)	0.77	(0.75, 0.79)	Section 5.4.12 Page 181	Reported EQ-5D utilities in line with NICE reference case.[102] Use of time to death utilities previously accepted in NICE TA319.[2]
[90, 180)	0.60	(0.52, 0.68)	0.64	(0.57, 0.70)	0.62	(0.57, 0.67)		
[30, 90)	0.50	(0.40, 0.59)	0.54	(0.44, 0.63)	0.52	(0.45, 0.58)		
<30	0.37	(0.15, 0.60)	0.47	(0.31, 0.64)	0.42	(0.28, 0.56)		

† 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.*

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 with those from the submission for ipilimumab as 2nd line treatment (TA268)[1] 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 21.

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 adverse events, 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.[48;87;99;109;112-114] However, none of these studies specifically reported on patients who had been previously treated with ipilimumab. From an updated search conducted in March 2015 no additional relevant cost studies were identified for inclusion. The searches conducted for resource use data and the selection criteria followed for the identification and inclusion of relevant studies are provided in Appendix 22 and Appendix 23, respectively. A summary presenting the details of the included studies is available in Appendix 24.

All included studies were in the UK setting. The MELODY study represents the largest single study of resource utilisation in melanoma (n=220).[87;112] 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.[48]

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

Based on feedback from the consulted clinical experts, the MELODY study is outdated with regards to the long-term survivor costs to reflect the resource utilisation of advanced melanoma patients previously treated within the NHS. Feedback from clinical experts was incorporated in the model to estimate resource utilisation of patients surviving in the long-term. Experts agreed that patients will undergo regular check-ups (including a scan).

- Surviving patients who have not progressed continue treatment and require regular check-ups every 3 months; after 2 years, it is reasonable to assume that check-ups are undertaken every 3-6 months.

- For patients who have progressed, check-ups will continue on a minimum of a 3-monthly basis until an alternative treatment option can be found or death occurs.

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 the anticipated licence, the model assumed that a 2mg/kg dose of pembrolizumab is to be 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, this was calculated using the patient weight distribution from the KEYNOTE-002 clinical trial. 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 72). The average number of vials of pembrolizumab required per patient was 3.6. This calculation used only the European patients from the KEYNOTE-002 trial to be most representative of the UK population.

Table 72.: Weight distribution and average number of vials (European patients) [20]

Pembrolizumab	% among males	% among females	Upper Target Dose	No. of vials
26-50 kg	2%	9%	100	2
51-75 kg	25%	68%	150	3
76-100 kg	63%	18%	200	4
101-125 kg	8%	5%	250	5
126-150 kg	3%	0%	300	6
151-175 kg	0%	0%	350	7
175-200 kg	0%	0%	400	8
201-225 kg	0%	0%	450	9
Mean Number of Vials per Patient (assuming no vial sharing)				3.6

BSC

BSC was defined as a combination of anti-cancer agents commonly prescribed in the UK (including dacarbazine and off-licence use of paclitaxel, carboplatin, cisplatin, interferon alfa-

2b, vindesine, and temozolomide) and potentially 'no treatment', reflecting the fact that after treatment with ipilimumab (and additionally, after a BRAF inhibitor for those $BRAF^{V600}$ mutation positive patients), not all patients may be treated with an anti-cancer therapy.

For the purpose of the de novo cost-effectiveness model, the chemotherapy arm from the KEYNOTE-002 trial was used as a proxy to reflect BSC in the UK in the base case in order to match the evidence available for efficacy, safety and quality of life. Previous submissions in metastatic melanoma used the MELODY study[112] to define UK BSC. However this study was conducted in a second-line population, where 1st line therapy would have been dacarbazine; therefore, the study likely underestimates the use of chemotherapy at this line of therapy in current clinical practice. Based on the feedback provided by the clinical experts in melanoma, whenever they felt compelled to use chemotherapy post-active treatment, it would be dacarbazine. Given the availability of alternative definitions for BSC (see Table 73), sensitivity analyses were conducted to reflect the impact of these alternative definitions.

Table 73: Best supportive care components

	% of patients - KEYNOTE-002 Trial	% of patients - MELODY study	% of patients – BSC = dacarbazine
No active treatment	0%	69.5%	0%
Dacarbazine	26.3%	18.8%	100%
Paclitaxel	16.4%	0%	0%
Paclitaxel when used with Carboplatin	24.6%	0%	0%
Carboplatin	7.6%	3.6%	0%
Interferon alfa-2b	0%	3.6%	0%
Vindesine	0%	4.5%	0%
Temozolomide	25.1%	0%	0%

The dosing schedule for the different components of BSC was taken from the KEYNOTE-002 trial in order to be in line with the efficacy included and is shown in Table 74 and Table 75. The mean body surface area from the KEYNOTE-002 trial was used to calculate the required dosing for BSC.

Table 74: Best supportive care dosing schedule

Drug	Days Between Administrations	Length of Administration Period (Days)	Length of Break Between Administrations (Days)	Freq of administration (cycles)	Source
Dacarbazine	21	Indefinite	-	3	TA268[1]

Drug	Days Between Administrations	Length of Administration Period (Days)	Length of Break Between Administrations (Days)	Freq of administration (cycles)	Source
Paclitaxel	7	42	14	1	TA268[1]
Paclitaxel + Carboplatin	7	42	14	1	TA268[1]
Carboplatin	21	Indefinite	-	3	TA268[1]
Interferon alfa-2b	2	Indefinite	-	1	TA268[1]
Vindesine	14	Indefinite	-	2	TA268[1]
Temozolomide	28	Indefinite	-	4	TA268[1]

Table 75: Best supportive care dosing requirements

Drug	Dose	Dose Units	Target Dose	Source
Dacarbazine	1000	mg/m2	1910	KEYNOTE-002 trial[20]
Paclitaxel	175	mg/m2	344.75	TA268[1]
Paclitaxel when used with Carboplatin	175	mg/m2	344.75	TA268[1]
Carboplatin	AUC = 5		221.85	TA268[1]
Interferon alfa-2b	6	MU	6	TA268[1]
Vindesine	3	mg/m2	5.91	TA268[1]
Temozolomide	1000	mg/m2	1930	TA268[1]

Based on the distribution of patients across different systemic therapies and, potentially, no treatment, the drug costs associated with BSC were estimated according to the proportion of patients assumed to be receiving different active therapies as part of BSC, the average dose administered per active treatment and the corresponding unit cost per dose.

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.

Number of administrations required, unit costs and total drug costs per treatment per cycle

As per the anticipated licence, patients are expected to be treated until progression. Therefore, PFS has used as a proxy for the time on treatment with pembrolizumab, with an adjustment based on actual treatment received within KEYNOTE-002. For this, dose interruption and early stopping due to toxicity were analysed from the KEYNOTE-002 data and incorporated into the model per administered cycle of pembrolizumab and chemotherapy. These analyses showed that, on average, 70.8% of patients on chemotherapy and 87.5% of patients on pembrolizumab received their expected doses.

The unit costs per pack or vial of treatment administered (either pembrolizumab or systemic therapies administered as part of BSC) are presented in Table 76, and the total drug costs per treatment per cycle once considering the actual number of administrations required per patient is presented in Table 77.

As there were very few patients receiving subsequent therapies within the KEYNOTE-002 trial and the positioning of pembrolizumab within the UK treatment pathway would be at the end-of-life (after other available, effective active treatments), the costs of subsequent therapies were not included within the model.

Table 76: 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
Dacarbazine	100mg vial	£3.29	eMIT: 100mg powder for solution for injection vials (£32.90 for pack of 10) [115]
	200mg vial	£4.29	eMIT: 200mg powder for solution for injection vials (£42.90 for pack of 10) [115]
	500mg vial	£16.49	eMIT: 500mg powder for solution for injection vials[115]
Paclitaxel	5mL vial	£3.65	eMIT: 30mg/5ml solution for infusion vials, Packsize 1[115]
	16.7mL vial	£7.64	eMIT: 100mg/16.7ml solution for infusion vials, Packsize 1[115]
	25mL vial	£11.58	eMIT: 150mg/25ml solution for infusion vials, Packsize 1[115]
	50mL vial	£21.94	eMIT: 300mg/50ml solution for injection vials, Packsize 1[115]
Carboplatin	5mL vial	£3.98	eMIT: 50mg/5ml solution for infusion vials, Packsize 1[115]
	15mL vial	£9.31	eMIT: 150mg/15ml solution for infusion vials, Packsize 1[115]

	45mL vial	£24.75	eMIT: 450mg/45ml solution for infusion vials, Packsize 1[115]
	60mL vial	£28.55	eMIT: 600mg/60ml solution for infusion vials, Packsize 1[115]
Interferon alfa-2b	1mL vial - 10 MU	£41.55	MIMs 2015[116]
	2.5mL vial - 25MU	£103.94	MIMs 2015[116]
Vindesine	5mg vial	£78.30	MIMs 2015[116]
Temozolomide	5mg cap	£6.52	eMIT[115]
	20mg cap	£11.12	eMIT[115]
	100mg cap	£44.70	eMIT[115]
	140mg cap	£60.70	eMIT[115]
	180mg cap	£83.10	eMIT[115]
	250mg cap	£106.08	eMIT[115]

Table 77: Final comparator treatment costs

Treatment	Cost when vial sharing is not allowed	Cost when vial sharing is allowed
Dacarbazine	£58.04	£42.22
Paclitaxel	£29.24	£25.21
Carboplatin	£116.21	£105.56
Paclitaxel (in combination with carboplatin)	£29.24	£25.21
Interferon alfa-2b	£41.55	£24.93
Vindesine	£156.60	£92.55
Temozolomide	£187.98	£187.98

Administration costs

Administration costs have been sourced from NHS reference costs[117] and are shown in Table 78. The base case costs used for administration are presented in Table 79.

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. [118]This was considered an appropriate approach as it was agreed with NHS England for EAMS patients.

BSC

The systemic chemotherapies comprised under BSC are all delivered intravenously as part of complex chemotherapy administration, as reported in previous submissions for metastatic melanoma.[1]

Table 78: NHS reference costs – administration of treatments[117]

Type	Source	Unit Price
Deliver simple parenteral chemotherapy at first - Outpatient	NHS Reference Costs 13/14 SB12Z-Outpatient	£164.81
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 subsequent elements of a Chemotherapy cycle - Daycase	NHS Reference Costs 13/14 SB13Z - Daycase	£327.75

Table 79: Administration Costs used in the model[117]

Treatment	Type of Administration Required	Daycase or Outpatient?	Cost
Pembrolizumab	Simple Chemotherapy	Daycase	£245.17
Dacarbazine	Complex Chemotherapy	Daycase	£316.95
Paclitaxel	Complex Chemotherapy	Daycase	£325.95*
Paclitaxel + Carboplatin	Complex Chemotherapy	Daycase	£325.95*
Carboplatin	Complex Chemotherapy	Daycase	£316.95
Interferon alfa-2b	Complex Chemotherapy	Daycase	£316.95
Vindesine	Complex Chemotherapy	Daycase	£316.95
Temozolomide	Oral Chemotherapy	Outpatient (first visit only)	£136.48

**Weighted average to reflect the cost associated with subsequent elements of the chemotherapy cycle of systemic therapies requiring more than one administration per cycle.*

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 unstable at present and identifying the standard of care that the target population is currently receiving is rather challenging. Moreover, there is 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 (TA268)[1] a micro-costing approach was implemented and the list of patient resource use was presented. Resource use data was sourced from the MELODY study.[112] 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.[87;112] This study had been commissioned and used as part of previous manufacturer's NICE submissions[1;2] 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[112] and from the manufacturer's submission for ipilimumab in 2nd line[1] and the corresponding unit costs used in this submission are presented in Appendix 25. 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, 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, an 'On treatment initiation' cost was applied during the first week of treatment.
  - Patient remaining without progression after treatment initiation were allocated a 'Pre-progression – Monthly' cost.
- For patients experiencing progression costs were differentiated between:
  - The one-off costs incurred when progression occurred (defined as 'Post-progression - One Off').
  - The subsequent monthly costs following the post-progression period (defined as 'Post-progression (not on treatment) Monthly' cost. The assumption made was that after progression, patients would receive palliative care but not active treatment, and therefore at this stage patients only incurred costs related to outpatient visits, inpatient stays and home care.
- Patients in the period just before dying were assumed to require palliative/terminal care, which was defined as 'Terminal Care - On Death' and related to the 90 days before dying. The costs of terminal care included services such as emergency inpatient admissions, non-emergency inpatient admissions, outpatient attendances and accident and emergency costs.[119]

Costs for BRAF mutation testing have not been included in the model as this takes place prior to this line of therapy.

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, nausea/vomiting, anaemia and neutropenia) 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. endocrine disorders or Grade 2 diarrhoea). The incidence of AEs for patients treated with pembrolizumab and BSC used in the model was obtained from KEYNOTE-002 (see section 4.12), and the unit costs were mainly derived from TA 319,[2] which referred to the MELODY study as the main data source (see Table 80). Leukopenia, hyponatremia and decreased platelet count were assumed to incur a null cost, as for previous submissions.[2;120]

Table 80: Adverse events costs

Adverse events	Items	Value	Source
Fatigue	Inpatient Cost & %	£586.38, 10%	Ipilimumab 1L submission[2] inflated to 2014 costs
	Outpatient Cost & %	£156.84, 90%	
	Average Cost per Patient	£200.79	
Diarrhoea	Inpatient Cost & %	£838.46, 50%	Ipilimumab 1L submission[2] inflated to 2014 costs
	Outpatient Cost & %	144.05, 50%	
	Average Cost per Patient	£491.25	
Nausea and vomiting	Inpatient Cost & %	£838.46, 10%	Assumed the same as diarrhoea
	Outpatient Cost & %	£144.05, 90%	
	Average Cost per Patient	£213.49	
Anaemia	Inpatient Cost & %	£586.38, 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[2] 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[2] inflated to 2014 costs
	Outpatient Costs & %	£205.01, 70%	
	Average Cost per Patient	£629.42	
Leukopenia	Cost assumed £0		Cost assumed £0

Adverse events	Items	Value	Source
Thrombocytopenia	Outpatient Cost and %	£316.00, 100%	NHS reference costs 2013/14[117] Thrombocytopenia Daycase SA12 K
	Average Cost per Patient	£316.00	
Hyponatremia	Cost assumed £0		Cost assumed £0
Platelet count decreased	Cost assumed £0		Cost assumed £0

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*

Summary of base-case de novo analysis inputs

5.6.1 Tabulated variables included in the cost-effectiveness analysis

Please find in Appendix 26 a table summarising 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 as closely as possible.

Assumptions

5.6.3 List of all assumptions used in the de novo economic model with justifications for each assumption

Table 81 summarised the assumptions used in the economic model.

Table 81: List of assumptions used in the economic model

Area	Assumption	Justification
Comparator	BSC (including dacarbazine) is the appropriate comparator and reflects UK clinical practice	MSD suggest it is appropriate to consider chemotherapy, including dacarbazine, as part of a BSC regimen for the reasons mentioned in section 1.1 (i.e. similar efficacy across chemotherapies (including dacarbazine) in respect to OS and PFS). The Melody study[87] supports BSC (including dacarbazine) being considered as reflecting UK clinical practice.

		As per the population of interest addressed in the key clinical trials supporting this submission, BRAF^{V600} mutation positive patients must have had a prior treatment regimen with an approved BRAF and/or MEK inhibitor.
Treatment pathway	Once patients progress they receive palliative care without systemic treatment	No more active treatment options are available after ≥2L treatment since BRAF wild type patients received ipilimumab as 1L treatment and then pembrolizumab as 2L, while BRAF mutation-positive would have been treated with a BRAF agent (as per expected license) in addition to ipilimumab.
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[1] 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 the refractory population from KEYNOTE-002 are applicable to the target population as for the anticipated license (i.e. ipilimumab-treated and ipilimumab-refractory populations, as included in KEYNOTE-001 and KEYNOTE-002 trials)	Refractory population is a sub-group of the treated population. KEYNOTE-002 trial (i.e. including refractory patients) is expected to underestimate the true OS benefit associated with use of pembrolizumab as survival benefit shown in refractory populations of both KEYNOTE-001 and KEYNOTE-002 is lower than the survival benefit of the treated population from KEYNOTE-001. The data available for the 2 mg dose was on the refractory population, which is a sub-group of the treated population anticipated in the license. The KEYNOTE-002 trial (i.e. including refractory patients) is expected to underestimate the true OS benefit associated with use of pembrolizumab as survival benefit shown in refractory populations of both KEYNOTE-001 and KEYNOTE-002 is lower than the survival benefit of the treated population from KEYNOTE-001.Therefore, the assumption is conservative.
Efficacy	Pembrolizumab expected to show a similar survival profile to ipilimumab in the long-term	The extrapolation of the pembrolizumab OS benefit is based on the long term follow-up for the ipilimumab treated arm as reported in the paper by Schadendorf 2015.[8] The approach was validated by melanoma clinical experts and supported by the preliminary results of the Phase III, KEYNOTE-006 randomised controlled trial.[14] Different extrapolation options have been considered in sensitivity analysis (see section 5.3.3.)
	Proportional hazards likely to hold in the long-term	The long-term survival with chemotherapy is instead thought to be down to the body's natural immune system. Immunotherapy works by activating the immune system thereby simulating the same type of response but in a greater proportion of patients
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 HRQL 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)[2] 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-002 trial was assumed to reflect that observed in practice	Assumption based on the results of the KEYNOTE-002 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).[1]
Costs	Long term survivors (>2 years) were assumed to require a check-up (including a scan) every 4 months (range: 3-6 months	Patients who progress may require more frequent scans if it is believed that an alternative treatment option can be found for the patient. However, given the position in the treatment pathway for the patients considered in this submission, it is likely that these patients have exhausted all treatment options and will receive only palliative care without additional check-ups. Based on feedback from three consulted clinical experts, long term costs for patients treated with either pembrolizumab or BSC and surviving above 2 years have been accounted for.

5.7 Base-case results

5.7.1 Base-case cost effectiveness analysis results

The results of the economic model are presented in Table 82 below. The estimated mean overall survival was 3.10 years for pembrolizumab and 1.51 years for BSC. At the end of the 30-year time horizon there were 0.9% patients still alive in the pembrolizumab cohort and 0.1% in the BSC cohort. Patients treated with pembrolizumab accrued 2.26 QALYs compared to 1.07 among patients in the BSC cohort. A table presenting a comparison of the clinical outputs estimated by the model and those obtained from the KEYNOTE-002 clinical trial is presented in Table 83.

5.7.2 Base-case incremental cost effectiveness analysis results

Table 82 below presents the base case incremental cost-effectiveness results incorporating our PAS. The results show pembrolizumab to be cost-effective compared to BSC when considering a willingness to pay threshold of £50,000 per QALY. As can be seen, considering a 30-year time horizon pembrolizumab resulted in 1.59 additional QALYs at an increased cost of £50,995. This represented a large net QALY gain (an increase of 111%) at an incremental cost per additional QALY gained of £42,923. This incremental-cost-effectiveness ratio (ICER) should be considered in the context of pembrolizumab being an end of life technology that presents an innovative nature (see Section 2.5).

Table 82: Base-case results (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£15,960	1.51	1.07	-	-	-	-
Pembrolizumab	£66,955	3.10	2.26	£50,995	1.592	1.188	£42,923
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

5.7.3 Clinical outcomes from the model

The outcomes of the pembrolizumab 2mg/kg and chemotherapy arms of the KEYNOTE-002 trial have been compared to the outcomes from the model in Table 83. The percentage of patients who had not progressed at 6 months was similar between the trial and the model, suggesting that in the short term the outcomes from the model are valid.

Table 83: Comparison of model and trial outcomes

Arm	Outcome	KEYNOTE-002	Model
Pembrolizumab	% patients with PFS at 6 months	34.3	34.8
BSC	% patients with PFS at 6 months	15.6	15.6

5.7.4 Markov traces

Table 84 and Table 85 below illustrate how patients move through the model states over time when treated with pembrolizumab or BSC, respectively. The diagrams show that patients spend longer in the pre-progression health state on pembrolizumab compared the BSC and that patients also survive for longer overall.

Table 84: Markov trace for pembrolizumab

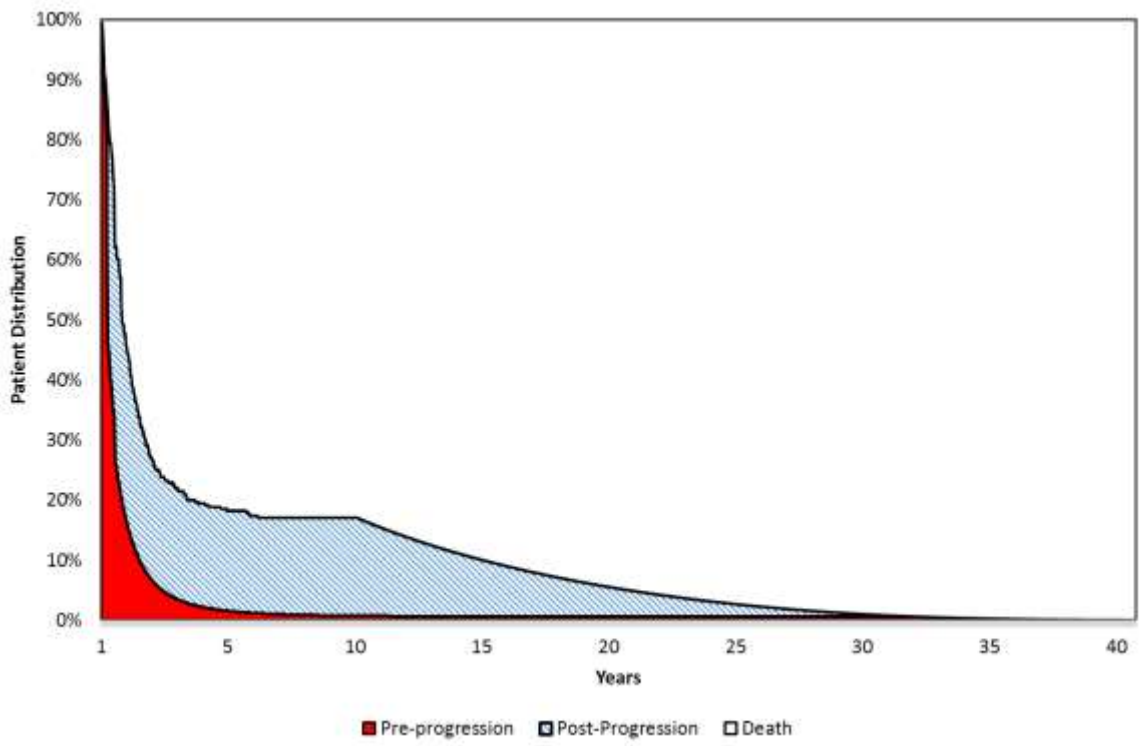
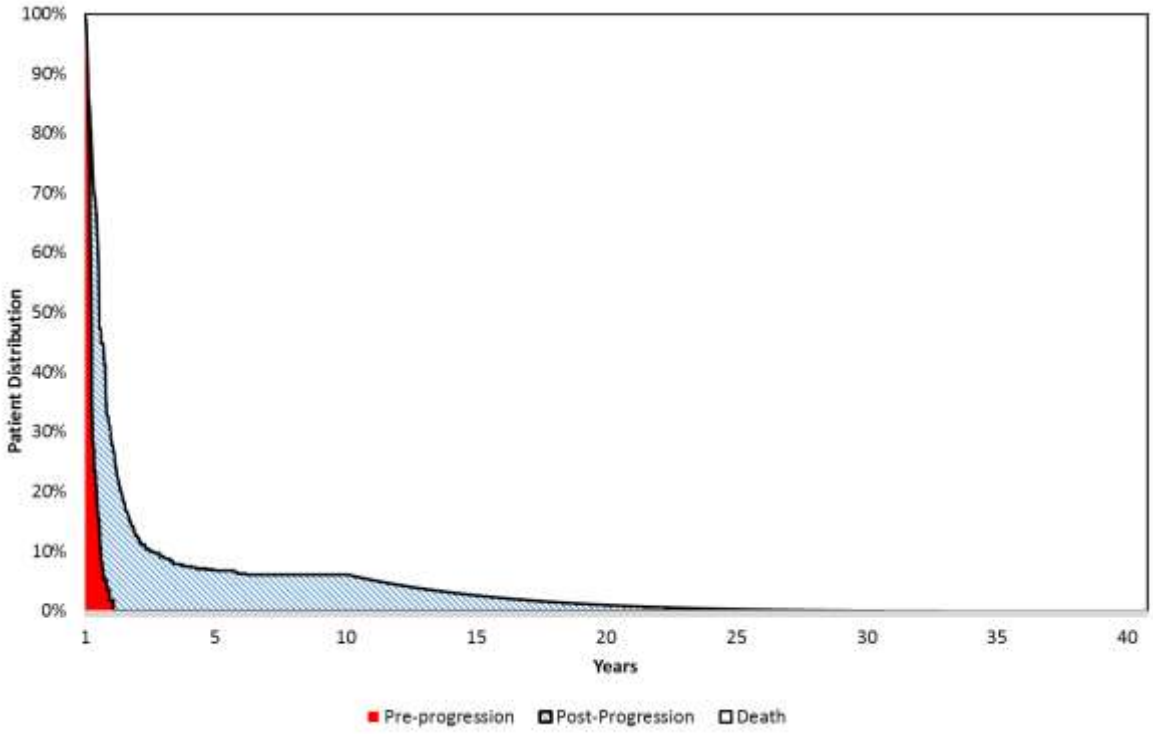


Table 85: Markov trace for BSC



5.7.5 Accruement of costs, QALYs and LYs over time

Figure 39, Figure 40 and Figure 41 shows how the costs, QALYs and life years accumulate over time, 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 39: Cumulative Costs over Time

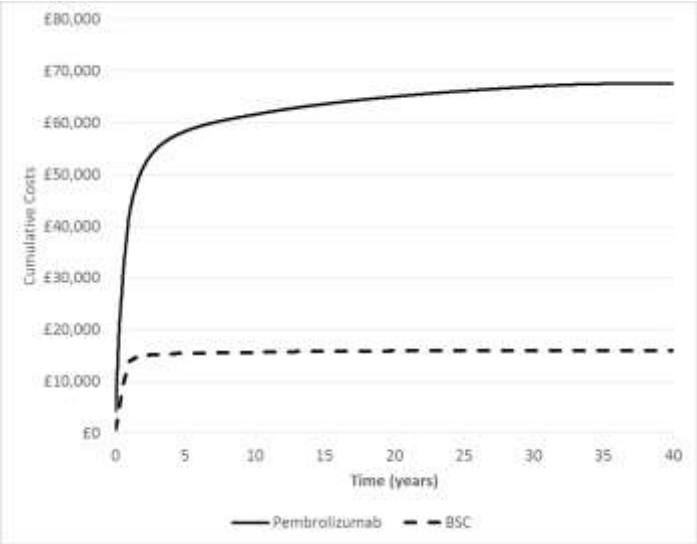


Figure 40: Cumulative QALYs over Time

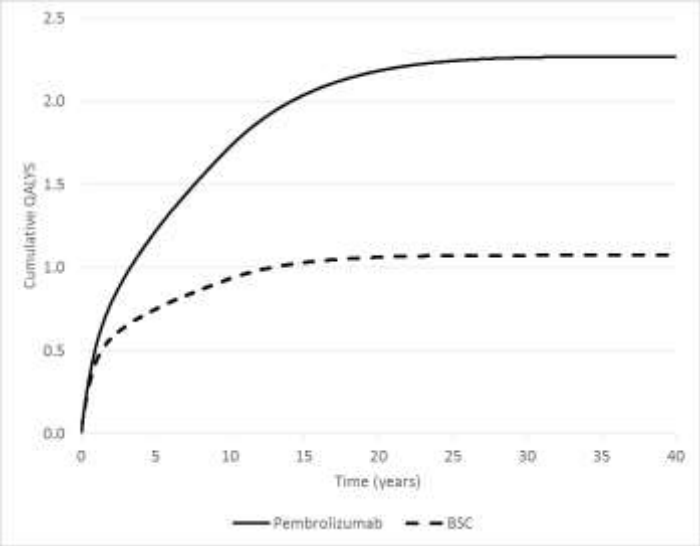
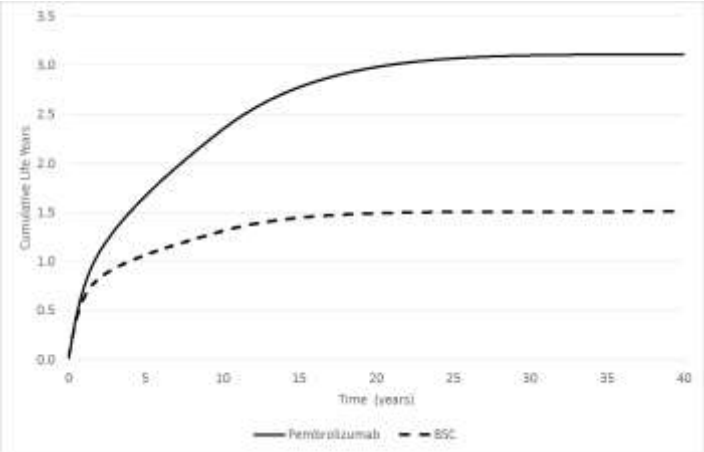


Figure 41: Cumulative LYs over Time



5.7.6 Disaggregated results of the base case incremental cost effectiveness analysis

Table 86 shows the disaggregated life years by health state. This shows that patients on pembrolizumab spend longer in both the pre and post progression health states compared to patients receiving BSC. Table 87 shows that the majority of costs in the pembrolizumab cohort are associated with treatment.

Table 86: Disaggregated life-years by health state

	Pembrolizumab	BSC	Incremental
Pre-progression	0.762	0.315	0.446
Post-progression	2.340	1.195	1.146
Total	3.102	1.510	1.592

Table 87: Summary of predicted resource use by category of cost

	Pembrolizumab	BSC	Incremental	Absolute increment	% absolute increment
Treatment Costs	£49,891	£475	£49,417	£49,417	95.86%
Admin Costs	£2,913	£1,795	£1,119	£1,119	2.17%
Pre Progression Costs	£1,891	£1,256	£636	£636	1.23%
Post Progression Costs	£8,036	£7,934	£102	£102	0.20%
Adverse Events Costs	£89	£99	-£10	£10	0.02%
Terminal Care Costs	£4,134	£4,403	-£269	£269	0.52%
Total	£66,955	£15,960	£50,995	£51,553	100.00%

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 was undertaken using 1000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix 26.

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 88. There is variation in the results both in terms of QALYs and costs between the two treatment arms.

Table 88: Incremental cost-effectiveness results based on probabilistic sensitivity analysis (discounted, with PAS)

	Total Costs	Total LYs	Total QALYs	Incremental costs	Incremental LYS	Incremental QALYs	ICER
BSC	£15,594	1.57	1.12				
Pembrolizumab	£92,741	3.10	2.25	£77,147	1.53	1.14	£67,615

The cost-effectiveness acceptability curve shows that there is an approximately 50% chance of pembrolizumab to be cost-effective when compared to BSC at the £50,000 per QALY threshold.

Figure 42: Scatterplot of PSA results (1,000 simulations; results discounted, with PAS)

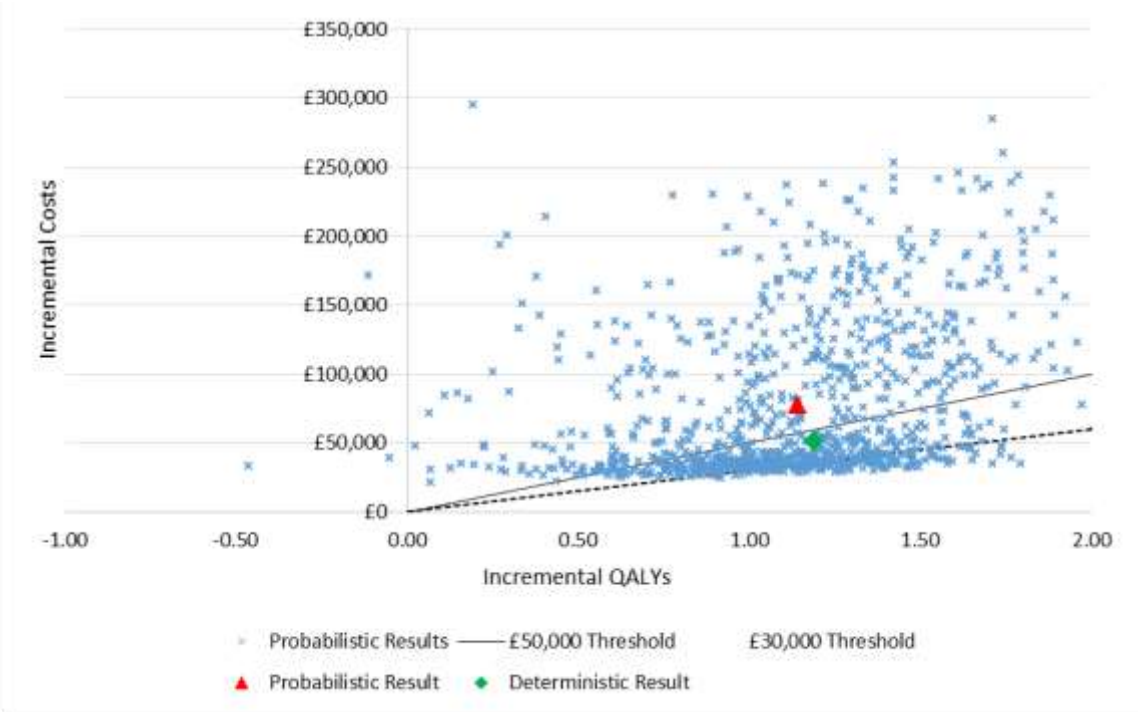
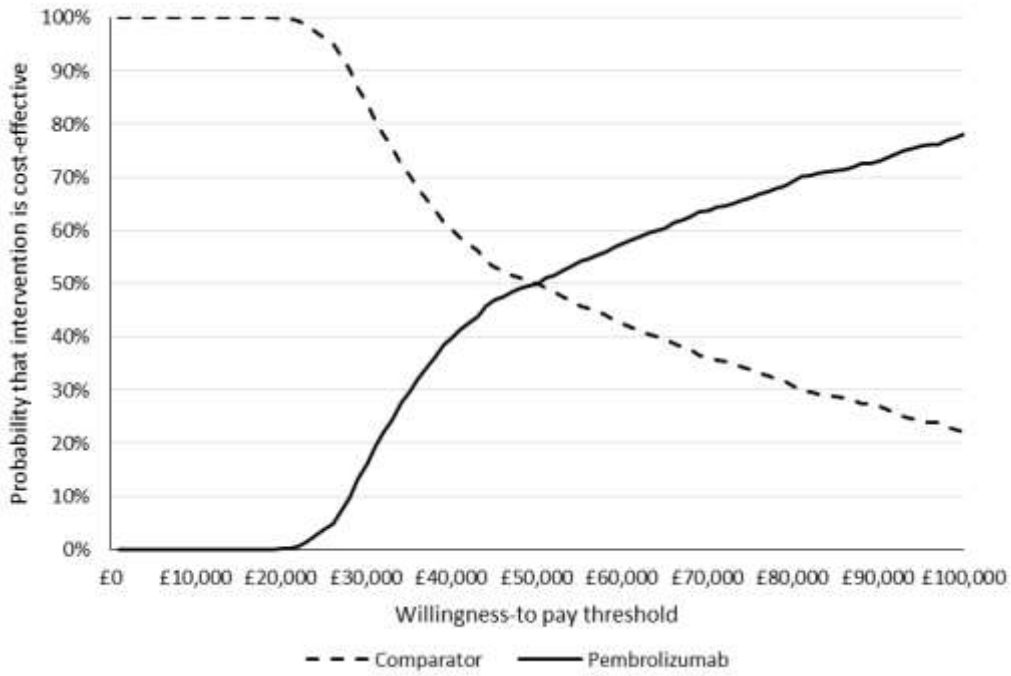


Figure 43: Cost-effectiveness acceptability curve (results discounted, with PAS)



The probabilistic mean ICER is significantly greater than the deterministic mean. This is due to the uncertainty in the relatively short-term PFS data from the KEYNOTE-002 clinical trial, meaning that in some samples a substantial proportion of patients are being treated for 20

years or more, with it being 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.[14] 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 Table 89.

Table 89: Incremental cost-effectiveness results based on probabilistic sensitivity analysis and maximum duration of therapy of 2 years[14] (discounted, with PAS)

	Total Costs	Total LYs	Total QALYs	Incremental costs	Incremental LYS	Incremental QALYs	ICER
Deterministic Result (including maximum duration of therapy of 2 years)							
BSC	£15,960	1.51	1.07				
Pembrolizumab	£53,698	3.10	2.26	£37,738	1.592	1.188	£31,764
Probabilistic Result (including maximum duration of therapy of 2 years)							
BSC	£15,497	1.60	1.14				
Pembrolizumab	£54,020	3.12	2.28	£38,523	1.527	1.138	£33,841

The probabilistic mean ICER is close to the deterministic result when a maximum duration of therapy of 2 years is considered (£33,841 compared to £31,764, respectively). This shows that the higher probabilistic mean ICER value and the large spread around the costs seen in Figure 42 is driven by responding patients receiving drug treatment for life. The associated scatterplot shows less variation around the simulated ICERs (see Figure 44) and the cost-effectiveness acceptability curve under this scenario shows that there is 87% chance of pembrolizumab being cost-effective when compared to BSC at the £50,000 per QALY threshold (see Figure 45), with a median ICER of £32,559.

Figure 44: Scatterplot of PSA results (1,000 simulations; results discounted, with PAS) considering a maximum duration of therapy of 2 years

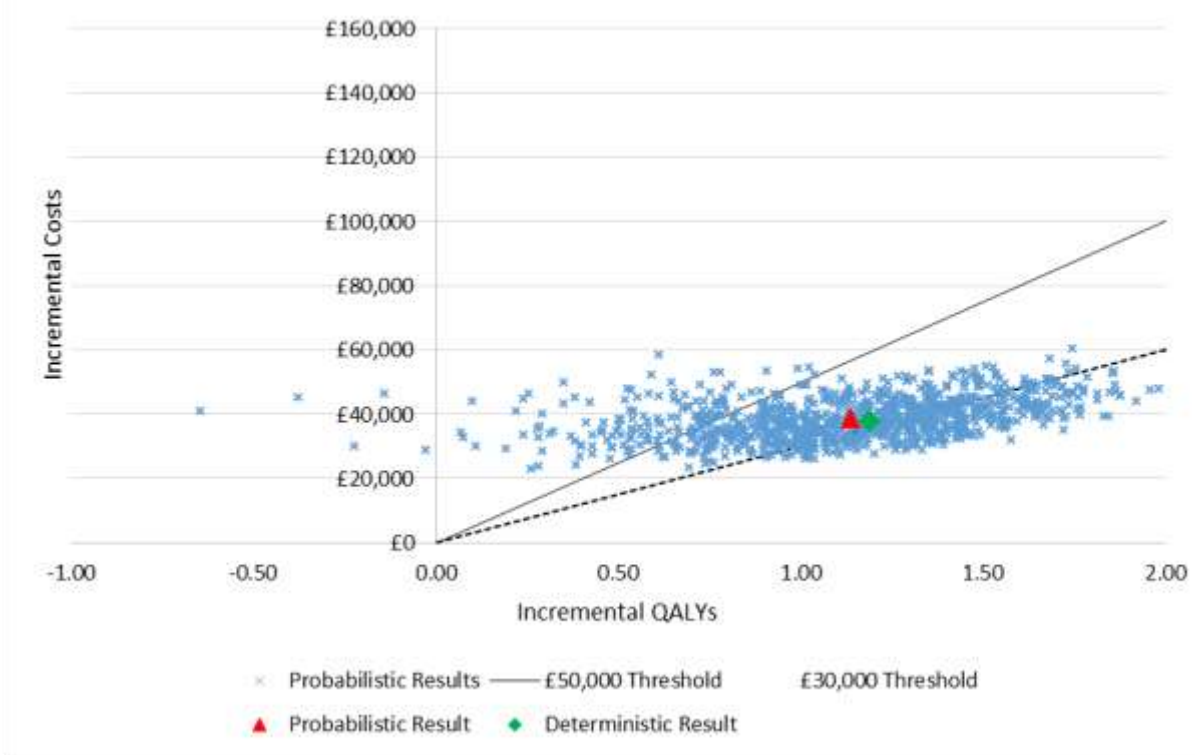
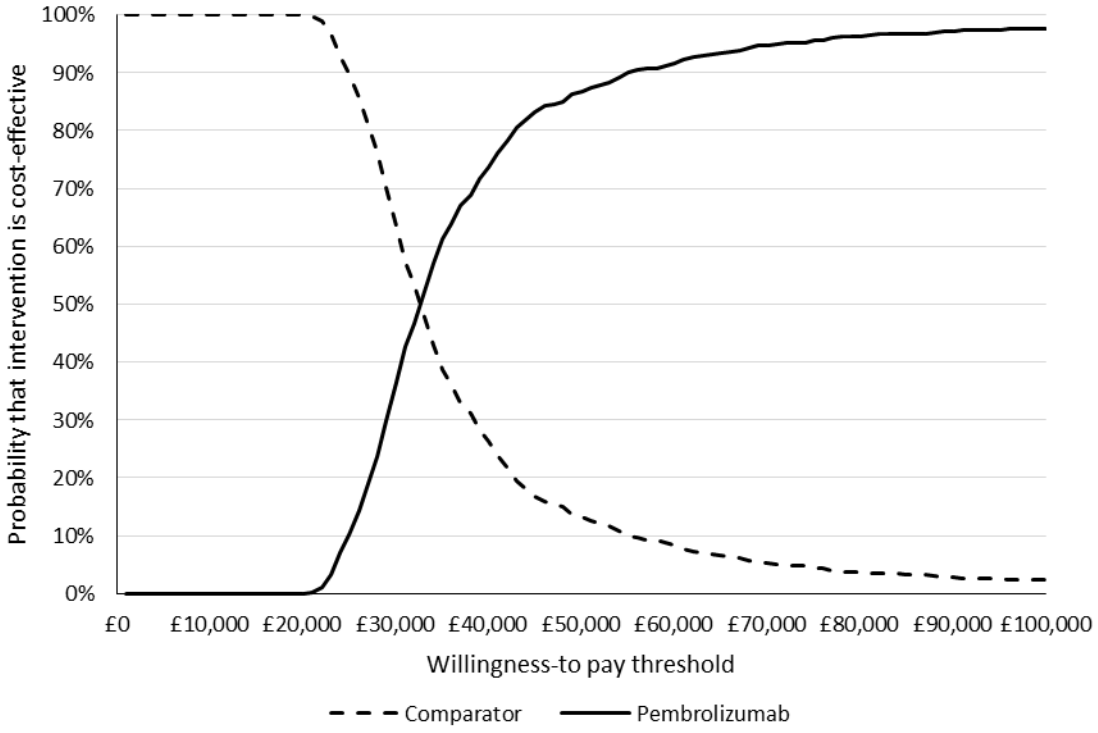


Figure 45: Cost-effectiveness acceptability curve (results discounted, with PAS) considering a maximum duration of therapy of 2 years



5.8.2 Deterministic sensitivity analysis

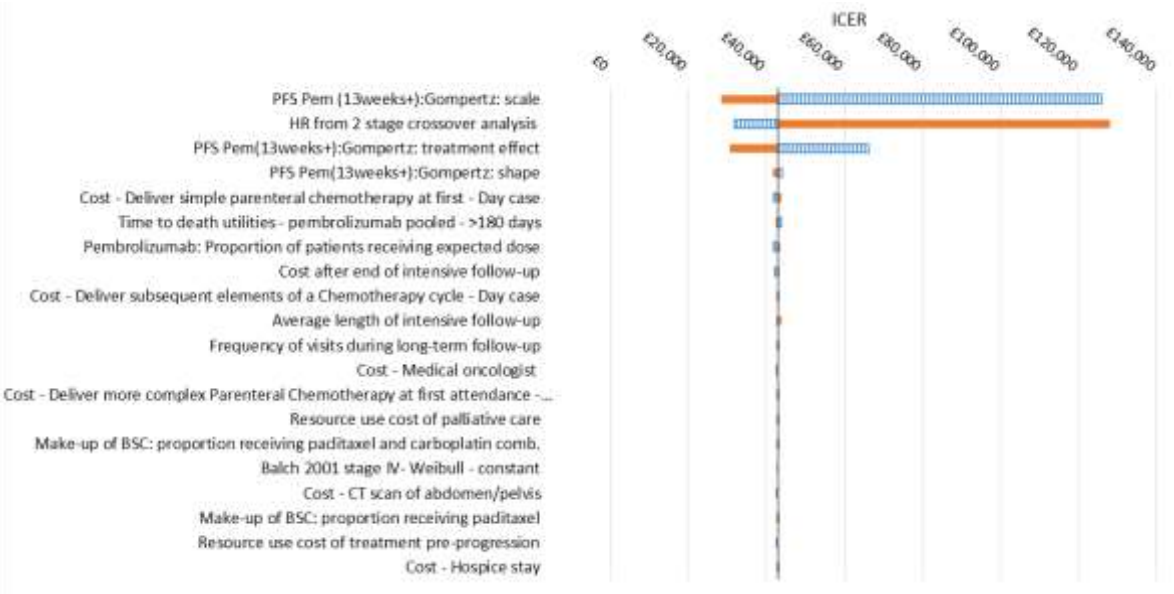
Deterministic sensitivity analysis was conducted for the following key variables using the 5% and 95% confidence intervals for the variables except when it is indicated otherwise:

- PFS curve coefficients
- HR for OS from the two-stage crossover adjustment
- Baseline characteristics (including patients' starting age, the proportion of male patients and the patients' average weight)
- Administration costs
- Follow-up resource utilization and unit costs
- Costs of terminal care
- Proportion of patients experiencing adverse events
- Costs of adverse events
- Time-to-death utilities

- Utility decrements for adverse events

Figure 46 presents the results of the deterministic sensitivity analyses. The input that most affects the ICER is the curve fit parameters assumed for PFS, as the majority of the benefits associated with pembrolizumab come from increased survival over BSC. The other variable that significantly affected the ICER was the HR for OS estimated from the two-stage crossover adjustment. The rest of the modified variables had a minor impact on the estimated ICER.

Figure 46: Tornado diagram presenting the results of the deterministic sensitivity analysis for the 20 most sensible variables (discounted results, with PAS)



5.8.3 Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions. Including:

- HR for OS from the crossover adjustment using the simple covariate adjustment for the two-stage model and the IPCW adjustment
- Alternative extrapolation scenarios to estimate PFS and long-term OS for BSC
    - For PFS, based on a two-part curve fit approach or on external data from the ipilimumab 2nd line submission (instead of KM data directly) or from external sources

    - For OS, using external sources of data derived from the ipilimumab 2nd line submission)

- Curve fit used for pembrolizumab PFS curve
- Utilities estimates based on progression-based health states and alternative sources for time to death utilities from ipilimumab 2nd line submission
- Age-related utility decrement
- Inclusion of adverse event disutilities
- Definition of BSC
- Time horizon
- Feasibility of vial sharing in clinical practice

Table 90 shows that the majority of scenarios assessed result in an ICER below the £50,000 threshold. The scenario analysis showed that the only scenarios which result in ICERs above the threshold are use of the log-normal and log-logistic curves for PFS and use of less robust shorter term data for extrapolation of long-term survival / projection of survival based upon assumption of proportional hazards between immunotherapy and chemotherapy and use of chemotherapy data long term. The PFS scenarios are clinically unrealistic as they project patients still on treatment at 20+ years and are not clinically valid as some patients do not progress. The alternative extrapolation scenarios presented are also considerably less clinically robust than the assumptions presented in the model base case as it is highly unlikely that pembrolizumab would demonstrate worse long-term outcomes than have been seen for ipilimumab. Scenarios presenting more realistic assumptions for long-term chemotherapy survival produce substantially lower ICERs than the model base case at £33,681 and £33,424.

The results from the scenario analysis show that the assumption made in the cost-effectiveness analysis have little impact on the ICER (see Table 90). Pembrolizumab is still cost-effective when considering alternative scenarios for the BSC definition, utility values used and crossover adjustment method.

Although the Log-normal and log-logistic curves gave greater estimates of the ICER, these are not realistic projections as in practice there are a number of patients who never progress (see Appendix 17).

Table 90: Results from the scenario analyses

			BSC			Pembrolizumab						
Parameter	**Base Case**	**Sensitivity Analysis**	**Total Costs**	**Total QALYs**	**Total LYs**	**Total Costs**	**Total QALYs**	**Total LYs**	**Incremental Costs**	**Incremental QALYS**	**Incremental LYS**	**ICER**
Base case	N/A	N/A	£15,960	1.07	1.51	£66,955	2.26	3.10	£50,995	1.19	1.59	£42,923
Varying the time horizon												
Time horizon	30 years	10 years	£15,649	0.93	1.31	£61,537	1.72	2.34	£45,888	0.79	1.03	£58,086
		20 years	£15,929	1.06	1.49	£65,009	2.18	2.98	£49,080	1.12	1.49	£43,888
Definition of BSC												
Source of BSC definition	Chemotherapy from KN002 trial	MELODY	£15,415	1.07	1.51	£66,955	2.26	3.10	£51,539	1.19	1.59	£43,382
		DTIC	£15,228	1.07	1.51	£66,955	2.26	3.10	£51,727	1.19	1.59	£43,539
Utilities												
Source of utility estimates	Time to Death utilities KN002: pooled utilities (2mg/kg and chemotherapy)	Time to Death utilities KN002: utilities by treatment arm	£15,960	1.06	1.51	£66,955	2.28	3.10	£50,995	1.22	1.59	£41,851
		Utilities based on pre and post progression KN002 – pooled over the 2 arms	£15,960	1.01	1.51	£66,955	2.07	3.10	£50,995	1.06	1.59	£48,056
		Time to death - 2nd line ipilimumab NICE submission (TA268)	£15,960	1.19	1.51	£66,955	2.45	3.10	£50,995	1.26	1.59	£40,471
		Utilities based on pre and post progression - 2nd line ipilimumab NICE submission (TA268)	£15,960	1.11	1.51	£66,955	2.29	3.10	£50,995	1.18	1.59	£43,218
Utilities decrement per year	From age of 60 to 75	No age-related disutility	£15,960	1.09	1.51	£66,955	2.33	3.10	£50,995	1.24	1.59	£41,240

			BSC			Pembrolizumab						
Parameter	**Base Case**	**Sensitivity Analysis**	**Total Costs**	**Total QALYs**	**Total LYs**	**Total Costs**	**Total QALYs**	**Total LYs**	**Incremental Costs**	**Incremental QALYS**	**Incremental LYS**	**ICER**
QALY decrement based on AEs experienced	Based on Beusterien et al disutilities from AEs reported in KN002 CSR and duration of AEs from Beusterien et al	No disutility associated with AEs (assuming disutility is already included within the trial data)	£15,960	1.07	1.51	£66,955	2.26	3.10	£50,995	1.19	1.59	£42,902
Treatment efficacy assumptions - pembrolizumab												
Crossover adjustment	two-stage approach with full covariate adjustment	two-stage approach with simple covariate adjustment	£15,899	1.06	1.49	£66,955	2.26	3.10	£51,056	1.20	1.61	£42,376
		IPCW approach	£16,422	1.21	1.69	£66,955	2.26	3.10	£50,533	1.05	1.41	£47,991
Overall survival	KM during 1st year and from year 1 assuming same relative rate of survival as ipilimumab (curve from previously treated patients) using Schadendorf 2015 followed by registry data (Balch 2001) and general population mortality after year 10 [three part curve fit]	KM during 1st year and from year 1 assuming same relative rate of survival as ipilimumab (curve from treatment-naïve patients) using Schadendorf 2015 followed by registry data (Balch 2001) and general population mortality after year 10 [three part curve fit]	£16,027	1.16	1.63	£67,066	2.41	3.30	£51,039	1.25	1.67	£40,855
		Assuming same relative rate of survival as ipilimumab using MDX010-020 data	£15,773	0.83	1.18	£66,540	1.74	2.40	£50,767	0.91	1.22	£55,813

			BSC			Pembrolizumab						
Parameter	**Base Case**	**Sensitivity Analysis**	**Total Costs**	**Total QALYs**	**Total LYs**	**Total Costs**	**Total QALYs**	**Total LYs**	**Incremental Costs**	**Incremental QALYS**	**Incremental LYS**	**ICER**
		Using HR from KN002 two-stage on external data using gp100 data	£16,101	0.74	1.07	£66,019	1.55	2.15	£49,918	0.81	1.08	£61,664
		Using HR from KN002 two-stage on external data using Korn data	£16,581	0.74	1.07	£65,866	1.47	2.04	£49,284	0.73	0.97	£67,713
PFS - curve fit	Gompertz	curve fit to KM data - weibull	£15,960	1.07	1.51	£58,334	2.26	3.10	£42,374	1.19	1.59	£35,667
		curve fit to KM data - exponential	£15,960	1.07	1.51	£55,590	2.26	3.10	£39,630	1.19	1.59	£33,357
		curve fit to KM data - Lognormal	£15,960	1.07	1.51	£89,016	2.26	3.10	£73,056	1.19	1.59	£61,492
		curve fit to KM data - log-logistic	£15,960	1.07	1.51	£96,840	2.26	3.10	£80,880	1.19	1.59	£68,078
PFS - chemotherapy	KM data	Curve fit (gompertz)	£15,960	1.07	1.51	£63,499	2.26	3.10	£47,539	1.19	1.59	£40,014
Vial sharing			£16,045	1.07	1.51	£66,955	2.26	3.10				
Vial sharing allowed	No	Yes	£15,918	1.07	1.51	£60,122	2.26	3.10	£44,205	1.19	1.59	£37,208
Comparator												
Dataset used for comparator arm	Chemotherapy arm from KN002 trial	Korn dataset	£15,823	0.74	1.07	£66,955	2.26	3.10	£51,132	1.52	2.03	£33,681
		gp100	£16,101	0.74	1.07	£66,955	2.26	3.10	£50,854	1.52	2.03	£33,424

5.8.4 Summary of sensitivity analyses results

The results of the probabilistic sensitivity analysis showed that there was uncertainty associated to both the estimation of the model outcomes and costs. The probability of pembrolizumab being cost effective at a £50,000 threshold was 50%, and 87% if treatment was assumed to continue for up to 2 years. The probabilistic results when considering maximum duration of therapy of 2 years gave a more realistic estimate and showed the probabilistic mean to be close to the base case ICER.

One-way sensitivity analysis showed the curve parameters associated with pembrolizumab PFS to have the greatest impact on the ICER. The hazard ratio from the crossover analysis was also shown to have an impact of the ICER.

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 ICERs above the end-of-life threshold were those using the log-normal and log-logistic curves for PFS or using less robust shorter term data for the extrapolation of long-term survival based upon assumption of proportional hazards between immunotherapy and chemotherapy. The PFS scenarios were unrealistic as they projected patients still on treatment after 20 years or more. The alternative extrapolation scenarios presented are also considerably less clinically robust than the assumptions presented in the model base case as it is highly unlikely that pembrolizumab would demonstrate worse long-term outcomes than have been seen for ipilimumab. Scenarios presenting more realistic assumptions for long-term chemotherapy survival produce substantially lower ICERs than the model base case at £33,681 and £33,424.

5.9 Subgroup analysis

No subgroup analyses were considered in the cost-effectiveness analysis.

One of the secondary outcomes of the KEYNOTE-002 study[71] 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 chemotherapy.

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 percentage of patients who are PD-L1 negative and have a durable response is not insubstantial and there was evidence of efficacy for these patients compared with chemotherapy. Given that the patients eligible for pembrolizumab as for this submission have access to few remaining treatment options that

do not result in a 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 2mg/kg and chemotherapy arms of the KEYNOTE-002 trial have been compared to the outcomes from the model. The percentage of patients who had not progressed at 6 months were very similar between the trial and the model (

Table 91), suggesting that in the short term the outcomes from the model are valid.

Table 91: Comparison of model and trial outcomes

Arm	Outcome	KEYNOTE-002 (% not progressed at 6 months)	Model (% not progressed at 6 months)
Pembrolizumab	Progression-free survival	34.3	34.8
Best supportive care	Progression-free survival	15.6	15.8

Comparing the KEYNOTE-002 outcomes to external studies

When comparing the results from the chemotherapy arm of the KEYNOTE-002 trial to other trial chemotherapy arms it can be seen that that the QALYs and LYs are lower when gp100 data is used compared to extrapolation of the chemotherapy arm of KEYNOTE-002; this is likely due to the approach taken for extrapolation of OS when using KEYNOTE-002 (assumption of proportional hazards to the pembrolizumab arm of the KEYNOTE-002 trial). As shown in Figure 37**Error! Reference source not found.**, in the short-term (where data is the most reliable) survival using KEYNOTE-002 chemotherapy and gp100 are near identical. The long-term survival observed with gp100, which was accepted as a proxy for UK BSC in TA268, is lower that the estimates based upon an assumption of proportional hazards in the long-term between immunotherapy and chemotherapy. It is therefore likely that the model base case overestimates the efficacy of chemotherapy and therefore the ICER.

Table 92: Comparison of KEYNOTE-002 BSC outcomes to external studies

	QALYs	LYs
Chemotherapy from KEYNOTE-002	1.07	1.50
Gp100 from MDX010-20	0.78	1.07

Comparing the model outcomes to outcomes from ipilimumab 2nd line submission

The outcomes of the model have been compared to the best supportive care and ipilimumab outcomes published in TA268.[1] The BSC life years and QALYs in BSC arm of the model are very similar to the BSC arms published in TA268. Outcomes expected for pembrolizumab are similar to those seen for ipilimumab in previously treated patients. This conservatively reflects the expectations seen in clinical consultation.

Table 93: Comparison of model outcomes to outcomes from ipilimumab 2nd line submission

	QALYs	LYS
TA286		
Best Supportive Care	1.01	1.33
Ipilimumab	2.38	3.19
Pembrolizumab model		
Best Supportive Care	1.07	1.50
Pembrolizumab	2.26	3.10

Expert validation

The model approach and inputs have 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 economic practice and methodology development in the UK and is a regular member of NICE ERG's. The model structure, selection of appropriate dataset, the survival analysis undertaken and assumption 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.

Opinion from an expert in crossover adjustment was sought to identify the most appropriate method to adjust for patients crossing over, after disease progression, from the chemotherapy arm to any of the pembrolizumab treatment arms. It was deemed that the two-stage approach method, using the time of progression as the secondary baseline, was potentially the most appropriate one to adjust for crossover.

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 anticipated licence. As mentioned previously (see section 5.3.1), the evidence considered for pembrolizumab was mainly derived from the KEYNOTE-002 trial, which assessed a refractory population reflecting a sub-group of the total ipilimumab-previously treated population anticipated in the licence. The OS estimated from KEYNOTE-002 data is expected to underestimate the true OS benefit associated with the use of pembrolizumab in the broader ipilimumab-previously treated population. Moreover, using KEYNOTE-002 data to estimate the OS associated with BSC was also conservative given that the alternative, external sources of evidence have estimated lower OS for the BSC / chemotherapy arms in populations with similar or better prognosis. Therefore, the economic evaluation is relevant to all groups of patients who could potentially use the technology, although it may underestimate the true benefit of pembrolizumab in the broader population eligible for treatment with pembrolizumab.

5.11.3 Generalisability of the analysis to the clinical practice in England

The population included in the KEYNOTE-002 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). However, as mentioned above and in section 5.3.2, patients included in the KEYNOTE-002 trial had more advanced disease than the population expected to be eligible for pembrolizumab in England (which is broader than that from KEYNOTE-002). This wider population of eligible patients is likely to experience greater survival than that observed from KEYNOTE-002.

In terms of the treatment pathway, no more active treatment options are available after second or third line treatments, in clinical practice in England, for BRAF wild type and $BRAF^{V600}$ mutation-positive patients, respectively. BRAF wild type patients would receive ipilimumab as 1st line treatment, while BRAF mutation-positive would be treated with a BRAF agent in addition to ipilimumab (as per expected license). Therefore patients would potentially receive pembrolizumab in second or third line, respectively, before they could be treated with pembrolizumab, with the remaining option being BSC. 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-002 trial comparing pembrolizumab to chemotherapy was used in the economic evaluation since it was deemed inappropriate to pool data from this trial with the KEYNOTE-001 trial data.

For the extrapolation of the results in the long term, appropriate external sources were used, whenever required, and data from patients previously treated 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 immaturity of data and 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 implications of these were tested in sensitivity analyses by taking into account alternative potential scenarios.

- Crossover:

Since crossover from the chemotherapy to pembrolizumab was allowed in the KEYNOTE-002 trial, the ITT analysis was substantially biased. Multiple crossover adjustment methods

were applied, following the recommendations from the NICE DSU, to reflect the true benefit of pembrolizumab compared to BSC / chemotherapy in the absence of crossover. The two-stage adjustment method was found to be the most appropriate for this adjustment, and it demonstrated a significant OS improvement for pembrolizumab compared to chemotherapy. Consistent results were obtained when the other potentially valid method (the IPCW) was implemented.

- Generalisibility to UK practice:

The main clinical evidence is derived from a refractory population, which represents a subgroup of the expected licence. This is likely to underestimate the OS benefit of pembrolizumab in the wider, eligible population.

- Assumption of proportional hazards:

Proportional hazards were assumed to generate the comparator arm data. This was necessary due to the immaturity of the data and the high levels of crossover. In the short-term this assumption was confirmed. In the long-term the assumption of proportional hazards was expected to overestimate the benefits of chemotherapy.

- Utillity values:

Utility values obtained from KEYNOTE-002 were lower than those reported in the submission of ipilimumab administered in second line.[1] This was justified on the basis that the KEYNOTE-002 refractory patients presented a poorer prognosis than those treated with ipilimumab in second line. This may have resulted in an underestimation of the number of QALYs and, consequently, an overestimation of the ICER presented in the base case analysis.

- Treatment duration:

There is uncertainty around the treatment duration of pembrolizumab. Patients are expected to be treated until progression (or discontinuation due to AEs), as for the anticipated license. However, 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.

Since the approaches taken for modelling are mostly considered to be conservative, the results here presented support the conclusion that within the context of innovative end-of-life therapies pembrolizumab is a cost-effective therapeutic option against the use of BSC for patients previously treated with ipilimumab and, if BRAFV600 mutation-positive, with a BRAF or MEK inhibitor.

5.11.5 Further analyses

The KEYNOTE-002 trial is an OS-event driven study that will be completed after 370 deaths. The evidence base for this economic analysis was derived from the second interim analysis of KEYNOTE-002, for which 220 deaths had occurred. A final analysis is expected to be available at the end of 2015. However, additional information from this final analysis is unlikely to add to what has been already presented here given the study design and the high levels of crossover observed in the trial. Therefore, MSD are unaware of any further analyses that could be performed with the existing available data to inform the current economic modelling approach.

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 who are BRAF^{V600} mutation positive and negative have been estimated as per the methodologies employed in the NICE costing template (NICE costing template TA269)[21] as reported in Table 94. The most recent England population estimates and melanoma incidence[121] have been used to calculate the aforementioned estimates.

Table 94: Estimates of incident population

Parameters	Estimate	Source
Total population - England	53,865,800	ONS Mid-2013 UK population estimates[122]
Incidence melanoma - England	0.0211%	Calculated (average of male and female)
	0.0210%	ONS cancer registration 2012 (released June 2014) – male[121]
	0.0212%	ONS cancer registration 2012 (released June 2014) - female[121]
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)[21]
Estimated number of incident patients stage IIIc-IV eligible for treatment in England in 2015	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)[123]
Proportion of patients who are BRAF^{V600} mutation-positive	48%	Long et al[124]
Proportion of patients who are BRAF^{V600} mutation-negative	52%	Calculated (1-proportion of patients who are BRAF^{V600} mutation positive)

The number of expected incident cases of malignant melanoma for 2015 in England is estimated to be 11,366, of whom 1,137 cases (10%) are expected to be stage IIIc and IV. Given current NICE treatment recommendations for unresectable or metastatic melanoma according to BRAF status, it is expected that 628 patients previously treated with ipilimumab

(and if being BRAF^{V600} mutation-positive, a BRAF or MEK inhibitor) will be eligible for treatment with pembrolizumab in 2015.

The eligible population to receive pembrolizumab treatment in 2nd line or 3rd line in the next 5 years has been estimated based on MSD forecasting and are presented in Table 95 and Table 96.

Table 95: Proportion of patients with BRAF mutation positive melanoma treated in 1L with either a BRAFi/MEKi or ipilimumab

Year	2015	2016	2017	2018	2019	2020
% treated with BRAFi* +/- MEKi in 1L	43.20%	37.70%	34.90%	34.30%	34.30%	34.30%
% treated with ipilimumab in 1L	16.30%	11.10%	8.60%	8.00%	7.90%	7.90%
Proportion of BRAF(+) not treated after BRAFi due to withdrawal (i.e. death, performance status or contraindication)						10.00%
Proportion of BRAF(+) not treated after BRAFi due to AEs						25.00%
Proportion of BRAF(+) not treated after ipilimumab due to withdrawal (i.e. death, performance status or contraindication)						10.00%
Proportion of BRAF(+) not treated after ipilimumab due to AEs						15.00%

**Vemurafenib or dabrafenib*

Table 96: Proportion of patients with BRAF wild type mutation treated in 1L with ipilimumab

Year	2015	2016	2017	2018	2019	2020
% treated with BRAFi* +/- MEKi in 1L	75.00%	21.90%	19.60%	19.60%	19.70%	19.70%
Proportion of BRAF(-) not treated after ipilimumab due to withdrawal (i.e. death, performance status or contraindication)						10.00%
Proportion of BRAF(-) not treated after ipilimumab due to AEs						15.00%

The estimated patient numbers for the BRAF mutation-positive patients treated with either BRAFi/MEKi or ipilimumab in 1st line have been estimated by applying the proportion of patients with BRAF mutation positive melanoma in 1st line with either BRAFi/MEKi or ipilimumab to the estimated number BRAF^{V600} mutation-positive patients.

The estimated patient numbers for the BRAF mutation-positive patients treated with either BRAFi/MEKi in 2nd line have been estimated by taking into account those who will withdraw after 1st line treatment and the proportion of BRAF mutation-positive that will be stop treatment after BRAFi due to AEs.[88]

The estimated patient numbers for the BRAF mutation-positive patients treated with ipilimumab in 2nd line have been estimated by applying to the estimated number of BRAF mutation-positive patients treated with ipilimumab in 1st line the proportion of BRAF mutation-positive that will be treated after ipilimumab due to withdrawal and the proportion of BRAF mutation-positive that will be treated after ipilimumab due to AEs.[88]

The total estimated number of BRAF mutation-positive patients eligible for pembrolizumab in 3rd line was estimated by summing up the BRAF mutation-positive patients treated with either BRAFi/MEKi or ipilimumab in 2nd line.

The BRAF mutation-negative patients treated with ipilimumab in 1st line was estimated by multiplying the percentage of BRAF wild type mutation patients treated in 1st line with ipilimumab to the $BRAF^{V600}$ mutation-negative patients. The total $BRAF^{V600}$ mutation-negative patients eligible for pembrolizumab in 2nd line was estimated by taking into account those withdrawing after ipilimumab and those who stopped treatment after ipilimumab due to AEs.

The estimated number of patients stage IIIc or IV eligible for treatment with pembrolizumab in 2nd or 3rd treatment line has been estimated by summing up the total $BRAF^{V600}$ mutation-positive treated with either BRAFi/MEKi or ipilimumab in 3rd line with the total $BRAF^{V600}$ mutation-negative patients eligible for pembrolizumab in 2nd line.

The estimated PD-1 class share comes from MSD internal forecasting[88] and has been used to estimate the total number of stage IIIc and IV patients eligible for pembrolizumab in 2nd or 3rd line treatment. We have not broken this down further to shares for individual drugs within the class (Table 97 and Table 98).

Table 97: Number of patients eligible for treatment with pembrolizumab in either 2L or 3L per year and BRAF status

	2015	2016	2017	2018	2019	2020
BRAF mutation-positive patients treated with either BRAFi/MEKi or ipilimumab in 1L						
With BRAFi/MEKi	261	236	226	230	238	246
With ipilimumab	99	69	56	54	55	57
BRAF mutation-positive patients treated with either BRAFi/MEKi or ipilimumab in 2L						
With BRAFi/MEKi	176	159	153	155	161	166
With ipilimumab	75	53	43	41	42	43
Total BRAF mutation-positive patients eligible for pembrolizumab in 3L						
	252	212	195	196	203	210
BRAF mutation-negative patients treated ipilimumab in 1L						
With ipilimumab	491	149	138	142	148	153
Total $BRAF^{V600}$ Mutation-negative patients eligible for pembrolizumab in 2L						
	376	114	105	109	113	117
Total stage IIIc and IV patients eligible for pembrolizumab in 2L or 3L						
	628	326	301	305	316	327

Table 98: Estimated maximum number of patients stage IIIc and IV treated with pembrolizumab in either 2L or 3L per year

	2015	2016	2017	2018	2019	2020
Estimated class share - PD-1 class	30%	57%	67%	69%	69%	69%
Estimated maximum number of stage IIIc and IV patients treated with pembrolizumab in 2L or 3L	**188**	**186**	**208**	**211**	**218**	**226**

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 2L or 3L are:

- Patients receive the licensed dose of 2mg/kg until disease progression.
- The following inputs are based on outcomes from KEYNOTE-002:
  - The mean treatment duration (in cycles)
  - The average number of vials per patients (with no vial sharing) used was based on European patient weights (detailed in section 5.5.2).
  - The proportion of patients receiving the dose expected
- All patients have been tested for $BRAF^{V600}$ mutation status[21]
- 0% are treated through clinical trials[21]
- 3.5% incidence change rates per year[2]

6.4 Assumptions that were made about market share in England

Market shares are based on MSD forecasting and applied to the BRAF mutation-positive and BRAF wild-type populations as explained in section 6.2 and presented in Table 95 and Table 96.[88]

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 pembrolizumab is administered at a dose of 2mg/kg every 3 weeks until disease progression or unacceptable toxicities. As mentioned in section 5 some patients may experience long-term survival. Mean overall survival is currently based on extrapolation method and the true mean overall survival observed in the population is not yet known. Although the assumptions used in the model are conservative there may be a significant number of patients treated with pembrolizumab who will be experiencing long term survival benefit and therefore long-term treatment with pembrolizumab.

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-outpatient: £164.81). [117]

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 BSC to subsequent treatment lines. The estimated budget impact on the NHS in England of all PD-1 agents is presented in Table 99. 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. £4,271,501).

Table 99: Estimated budget impact over 5 years

	2015	2016	2017	2018	2019	2020
Total stage IIIc and IV patients treated with PD-1 class for 2L or 3L	**188**	**186**	**208**	**211**	**218**	**226**
Total costs for PD-1 class	**£45,362**	**£45,362**	**£45,362**	**£45,362**	**£45,362**	**£45,362**
Total treatment costs	£25,290	£25,290	£25,290	£25,290	£25,290	£25,290
Total administration costs	£19,983	£19,983	£19,983	£19,983	£19,983	£19,983
Total adverse event costs	£89	£89	£89	£89	£89	£89
Maximum budget impact for pembrolizumab	**£8,543,002**	**£8,431,593**	**£9,133,511**	**£9,554,011**	**£9,889,787**	**£10,235,929**

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.

a number of assumptions were made in terms of proportion of patients treated in 1st and 2nd line, and on the patients that continued treatment to subsequent therapies after progression, which introduced uncertainty into the estimates here presented.

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