Evidence Review Group's Final Report
Ipilimumab for previously untreated unresectable malignant melanoma

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List of abbreviations

AE	Adverse event
AJCC	American Joint Committee on Cancer
BSC	est supportive care
CEA	Cost-effectiveness analysis
CFB	Change from baseline
CHE	Centre for Health Economics
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
DTIC	Dacarbazine
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ	European Organisation for Treatment of Cancer Quality of Life Questionnaire
ERG	Evidence Review Group
FDA	Food and Drug Administration
Gp100	glycoprotein 100 vaccine
HR	Hazard Ratio
HRQoL	Health related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
Ipi	Ipilimumab
irAE	Immune-related adverse event
ITT	Intention to treat
kg	Kilogram
KM	Kaplan-Meier
LDH	lactate dehydrogenase
mg	Milligram
MS	Manufacturer’s submission
MTC	Mixed treatment comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported

OS	Overall survival
PAS	Patient Access Scheme
PFS	Progression free survival
PS	Performance status
PSA	Probabilistic Sensitivity Analysis
PSS	Personal social services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SEER	Surveillance Epidemiology and End Results Program
SPC	Summary of product characteristics
STA	Single Technology Appraisal
ULN	Upper limit of normal

1 Summary

1.1 Critique of the decision problem in the manufacturer's submission

Ipilimumab (Yervoy®) is a fully human monoclonal immunoglobulin antibody (IgG1κ) that stimulates the body's own immune system to fight cancer. In December 2012 ipilimumab was recommended by NICE as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy (TA268).[1] In August 2012 the manufacturer submitted an application to the European Medicines Agency (EMA) to extend the indication of ipilimumab to previously untreated adult advanced melanoma patients, which was approved in October 2013.[2] The recommended induction regimen of ipilimumab is 3 mg/kg administered as intravenous infusion over a 90-minute period every three weeks for a total of four doses.[3]

The manufacturer's decision problem matched the NICE scope in terms of the population, intervention, comparators and outcomes of interest.[4] First-line therapies currently used in the NHS include dacarbazine (DTIC) and the BRAF inhibitor vemurafenib. However, the MS also included dabrafenib as a comparator, which is currently scheduled for a NICE technology appraisal (ID605). Dabrafenib does not meet the reference case for comparators, defined as 'therapies routinely used in the NHS, including technologies regarded as current best practice'.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

There was no direct evidence for the clinical effectiveness of ipilimumab 3 mg/kg monotherapy compared with DTIC, vemurafenib or dabrafenib for the treatment of previously untreated, advanced melanoma patients.

Instead, the evidence the manufacturer focussed on came from four randomised controlled trials (RCTs). A large double-blind RCT demonstrated that ipilimumab 10 mg/kg plus DTIC (including a maintenance phase of ipilimumab therapy) significantly increased overall survival compared with DTIC plus placebo, in patients with previously untreated, advanced melanoma (CA184-024).[5] Median overall survival was increased by 2.1 months (11.2 months versus 9.1 months; $p<0.001$). Adverse events were more common in patients who were taking ipilimumab plus DTIC than DTIC plus placebo.

A small open-label RCT compared ipilimumab 3 mg/kg plus DTIC with ipilimumab alone for the treatment of chemotherapy-naïve metastatic melanoma patients (MDX010-08).[6] The results of this trial suggest that ipilimumab plus DTIC is more effective than ipilimumab alone (overall survival 14.3 months versus 11.4 months), although the trial was under powered to detect a statistically significant difference for this outcome.[6]

A large RCT of vemurafenib compared with DTIC for the treatment of previously untreated, BRAF V600 mutation positive advanced melanoma patients (BRIM-3) demonstrated that vemurafenib significantly increased overall survival compared with DTIC.[7] Median overall survival was increased by 3.6 months (13.2 months versus 9.6 months; p<0.001).

A reasonably large RCT compared dabrafenib with DTIC for the treatment of BRAF V600 mutation positive advanced melanoma patients who had not received previous antitumour therapy (other than interleukin-2) (BREAK-3).[8] However, data from the BREAK-3 trial were not mature enough to demonstrate a significant difference in overall survival; the median duration of follow-up for patients receiving dabrafenib was only five months. Dabrafenib was not included in NICE's scope and decision problem and is not currently routinely used in the NHS.

The MS also presented the interim results from two ongoing retrospective observational studies of ipilimumab 3 mg/kg for the treatment of previously untreated, advanced melanoma patients (CA184-332 and CA184-338)[9, 10] and a pooled analysis of treatment-naïve or chemotherapy-naïve advanced melanoma patients who were included in four RCTs (MDX010-08, CA184-004, CA184-022 and MDX010-020).[11]

Indirect and mixed treatment comparisons of ipilimumab, vemurafenib and dabrafenib

The MS included indirect comparisons and a mixed treatment comparison of ipilimumab (10 mg/kg) plus DTIC compared with vemurafenib and dabrafenib using the CA184-024,[5] BRIM-3[7] and BREAK-3[8] trials. The pair wise indirect comparisons using the Bucher equation showed no significant differences in survival between ipilimumab plus DTIC and the BRAF inhibitors vemurafenib (indirect hazard ratio 1.16, 95% CI 0.86 to 1.56) and dabrafenib (indirect hazard ratio 1.18, 95% CI 0.48 to 2.93). The mixed treatment comparison analysis of the network of evidence also demonstrated no significant difference in survival.

The MS acknowledged that there were a number of limitations with the indirect and mixed treatment comparisons, including the differences in patient characteristics and study design between the trials. In addition, there are differences in the mechanism of action between ipilimumab and BRAF inhibitors, resulting in different Kaplan-Meier curve shapes for overall survival, so the hazard ratios across trials may not be proportional.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The MS included a systematic review that, despite some methodological limitations, does not appear to have missed any relevant RCTs. Adequate study details were presented and the quality assessment was appropriate.

The CA184-024 trial was a large good quality RCT with reliable results, however this trial does not provide direct evidence for the effectiveness of ipilimumab 3 mg/kg monotherapy (without maintenance therapy) compared with DTIC, vemurafenib or dabrafenib for the treatment of previously untreated, advanced melanoma patients.

The MDX010-08 trial was under powered to detect a statistically significant difference in overall survival,[6] and the BREAK-3[8] and BRIM-3[7] trials of dabrafenib and vemurafenib were reasonably good quality, although they were both open-label and had a relatively short duration of follow-up.

The quality of the non-RCT studies was generally adequate;[9-11] however, there is a high risk of bias associated with these study designs, relative to an RCT. The manufacturer compared the results of the non-RCT studies with the DTIC arm of the CA184-024 trial,[5] however this is problematic due to the differences in patient characteristics and study design; there was also some double-counting of patients between the pooled dataset and the RCT evidence presented. The ERG does not consider that these studies provide additional relevant reliable data.

Superseded — see

The ERG does not consider the indirect comparisons or mixed treatment comparison of ipilimumab plus DTIC, vemurafenib and dabrafenib to be appropriate because of differences in patients' baseline characteristics between the trials (see below).

The ERG has three main concerns with the argument presented in the MS.

Erratum

Comparability of trial populations

The main ipilimumab trial population differs from the population included in the vemurafenib and dabrafenib trials (which are restricted to patients who are BRAF V600 mutation positive); these trials were used in the indirect and mixed treatment comparisons. There were differences in patients' baseline characteristics between the BRIM-3 and BREAK-3 trials and the CA184-024 trial; patients in the BRAF mutation-positive trials had a worse prognosis (differences in the proportion of patients with elevated serum lactate dehydrogenase levels and M1c disease).

Assumption of equivalent clinical effectiveness of ipilimumab monotherapy versus ipilimumab plus DTIC

The MS cites study MDX010-08 as evidence for the equivalence of ipilimumab monotherapy and ipilimumab plus DTIC.[6] However, the results of this very small (n=64 patients) trial suggest that ipilimumab plus DTIC may be more effective than ipilimumab alone. Therefore, there is no conclusive evidence that ipilimumab monotherapy is as clinically effective as ipilimumab plus DTIC.

Assumption of equivalent clinical effectiveness of 3 mg/kg versus 10 mg/kg dose

The MS seeks to demonstrate that a 3 mg/kg dose of ipilimumab is equivalent to a 10 mg/kg dose in terms of overall survival, using data from trials that were not included in the systematic review. In the CA184-022 RCT of previously treated and untreated patients, response rate (11.1% versus 4.2%), median overall survival (11.4 months versus 8.7 months) and progression-free survival (18.9% versus 12.9%) were all better in the 10 mg/kg treatment group, compared with the 3 mg/kg treatment group.[12] However, median overall survival was not statistically significantly different between the 10 mg/kg group and the 3 mg/kg group (HR 0.875, 95% CI 0.593 to 1.291). A very small trial of previously treated and untreated patients (CA184-004) concluded that there were no meaningful differences in clinical activity between the two ipilimumab doses.[13] In the manufacturer's response to the ERG's points for clarification document, the manufacturer presented the results of a pooled data analysis in both previously treated and untreated patients, which also suggested that a 10 mg/kg dose is better than a 3 mg/kg dose in terms of overall survival.[14] The FDA report[15] and EMA report[16] also highlighted the lack of evidence for the most clinically effective dose of ipilimumab and suggested the currently ongoing CA184-169 trial,[17] comparing ipilimumab 3 mg/kg with 10 mg/kg. Therefore, there is currently no conclusive evidence that ipilimumab at a dose of 3 mg/kg is as clinically effective as a dose of 10 mg/kg.

Based on the evidence presented, the ERG considers that the survival benefit may be overestimated in the MS. In view of the uncertainty of the survival estimate used in the manufacturer's economic model, the ERG have undertaken additional analyses to estimate the survival benefit of ipilimumab monotherapy at a dose of 3 mg/kg for patients with previously untreated, advanced melanoma. These are presented in the Section 6.3.1 of this report.

1.4 Summary of cost effectiveness evidence submitted by the manufacturer

No previously published cost-effectiveness studies of ipilimumab as a first-line treatment for advanced (unresectable or metastatic) malignant melanoma were identified by the manufacturer. Therefore, the manufacturer submitted a *de novo* analysis to estimate the cost-effectiveness of ipilimumab in two separate populations: BRAF V600 mutation-positive patients, who are eligible for first-line treatment with ipilimumab, DTIC, or vemurafenib; and BRAF V600 mutation-negative patients, who are eligible for first-line treatment with ipilimumab or DTIC. The cost-effectiveness of first-line therapy was assessed by using a treatment sequencing approach which incorporated second-line active therapy and third-line best supportive care (BSC). The transitions to second- and third-line treatment were modelled based on progression-free survival data, while overall survival data was used to model transitions to death. The modelled treatment pathways for ipilimumab were first-line ipilimumab followed by either BSC in the mutation-negative population or vemurafenib followed by

BSC in the mutation-positive population. The modelled pathway for DTIC in both sub-populations was first-line DTIC followed by second-line ipilimumab and third-line BSC. The modelled pathway for vemurafenib was first-line vemurafenib followed by second-line ipilimumab and third-line BSC in the mutation-positive population.

The assessment of cost-effectiveness was based on comparative effectiveness evidence on the efficacy of ipilimumab 10mg/kg in addition to DTIC therapy compared with DTIC therapy alone from the CA184-024 trial,[5] and the separate, independent arm from the BRIM-3 trial was used for vemurafenib.[7] The transitions between lines of treatment and the proportion of patients who die in each weekly cycle of the model were informed by extrapolated empirical data on overall survival (OS) and progression-free survival (PFS) from the clinical trials. For second-line treatments, OS was based on first-line survival curves but adjusted downwards to account for poorer outcomes on second-line therapy using a constant proportional hazard derived from expected life years of second-line ipilimumab (TA268).[1] The duration of response to second-line treatments was based on the number of pre-progression life years for second-line ipilimumab. Third-line treatment was assumed to be BSC, which consisted of a proportion of patients on 'no treatment' and a proportion on commonly prescribed chemotherapy drugs, including DTIC. The OS for patients who survived to receive third-line BSC was assumed to be the same as those on first-line treatment who had not progressed to next line of therapy. Quality of life was quantified by applying utility weights based on time-to-death, derived from the EORTC QLQ-C30 questionnaire data from CA184-024[5] in order to estimate quality-adjusted life years (QALYs). Costs were assessed from an NHS and personal and social services perspective and incorporated acquisition, administration and monitoring costs of the alternative regimens, adverse events and other supportive care and terminal care costs associated with the management of progressed disease.

Superseded – see Erratum

The manufacturer presented separate pair-wise comparisons of the incremental cost-effectiveness ratio (ICER) for ipilimumab with DTIC in the mutation-negative (£16,958 per QALY) and –positive populations (£31,559 per QALY) and ipilimumab with vemurafenib in the mutation-positive population (ipilimumab dominates vemurafenib with less costs and more QALYs). The manufacturer also presented results based on a pooled chemotherapy-naïve dataset (from CA184-004,[13] CA184-022,[12] MDX010-08,[6] MDX010-020[18] clinical trials), which showed similar and consistent ICERs to the base-case analysis. The manufacturer presented a series of one-way deterministic sensitivity analyses and scenario analyses to assess the impact of uncertainty around key input variables and assumptions on the ICER estimates. The results of these indicated that the base-case ICER estimates were most sensitive to the assumptions used to model overall survival of ipilimumab and DTIC, time spent on second-line treatments, and time spent on first-line treatment with ipilimumab relative to DTIC. The manufacturer's probabilistic sensitivity analysis concluded that the probability of

ipilimumab being the most cost-effective treatment compared with DTIC was 96% at a willingness to pay threshold of £50,000 per additional QALY and 40% at a threshold of £30,000 per QALY, while it was close to 100% for the comparison with vemurafenib.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the manufacturer's base-case ICERs to be both highly uncertain (largely due to the assumptions employed by the manufacturer for overall survival on second- and third-line treatments) and overly optimistic towards ipilimumab. The main driver of cost-effectiveness for the comparison of ipilimumab with DTIC and vemurafenib is the assumptions around the sequencing of treatments. The ERG considers the approach used by the manufacturer to estimate OS on second-line treatments and third-line BSC as arbitrary. The manufacturer switches between different OS curves at different lines of treatment such that overall survival on BSC is often better than on second-line treatment. The method used by the manufacturer is not consistent or clinically plausible, and substantially favours the cost-effectiveness of ipilimumab. The cost-effectiveness of ipilimumab is achieved by assuming that patients who progress to BSC following first-line ipilimumab achieve the long-term benefits of sustained overall survival from ipilimumab first-line. However, for the comparator treatment (DTIC or vemurafenib) patients who receive ipilimumab second-line cannot continue to receive the long-term benefits of sustained overall survival from ipilimumab second-line when they progress to BSC, instead they return to the lower overall survival of the first-line treatment (DTIC or vemurafenib).

Superseded – see Erratum

The model also makes a number of important assumptions about the relative efficacy of the treatments. The manufacturer's submission assumes that the absence of evidence for the licensed dose of ipilimumab 3mg/kg in previously untreated advanced melanoma implies equal efficacy to ipilimumab 10mg/kg, and that concomitant DTIC therapy with ipilimumab 10mg/kg in the CA184-024 trial[5] implies equal efficacy to ipilimumab 10mg/kg monotherapy. Furthermore, the model assumes that the use of separate, independent arms from different clinical trials (i.e. breaking randomisation) is sufficient to establish the relative efficacy of ipilimumab with vemurafenib. The model also employs higher acquisition costs of ipilimumab per weekly cycle when treated second-line compared with first-line, which ultimately disadvantages the comparator treatment where ipilimumab is received second-line. The ERG considers that these critical assumptions have not been robustly justified by the manufacturer and are not clearly supported by the existing evidence.

The ERG believes that the only plausible model structure on which to base the estimates of cost-effectiveness of ipilimumab is to consider first-line treatments only, which essentially uses a conventional three-state model based on pre-progression, post-progression, and death, with BSC being the only second-line treatment considered. This approach is consistent with that used in the previous appraisal of ipilimumab (TA268).[1]

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The evidence presented for the effectiveness of ipilimumab was identified through a reasonable quality systematic review. Whilst no direct evidence was identified for the clinical effectiveness of 3 mg/kg ipilimumab for previously untreated advanced melanoma, the RCT evidence presented in the MS was generally good quality.[5-8] The trial comparing ipilimumab 10 mg/kg plus DTIC with a relevant comparator (DTIC) for previously untreated advanced melanoma patients was well conducted and the results are likely to be reliable.[5]

Whilst there is a lack of direct evidence of the clinical effectiveness of 3 mg/kg ipilimumab monotherapy for the treatment of previously untreated advanced melanoma patients, the available RCT evidence (both first-line and second-line) consistently demonstrates increased overall survival with ipilimumab compared with DTIC or gp100 vaccine.[5, 18]

The ERG considered the manufacturer's economic submission to meet the requirements of the NICE reference case. Although the ERG does not consider the economic model structure based on sequencing of treatments sufficient to address the decision problem, the model does allow the possibility of 'turning off' the treatment sequencing part to allow a direct comparison of first-line ipilimumab with DTIC or vemurafenib in terms of OS and PFS in previously untreated patients.

1.6.2 Weaknesses and areas of uncertainty

There is currently no conclusive evidence that ipilimumab at a dose of 3 mg/kg is as clinically effective as a dose of 10 mg/kg. It was a condition of the EMA marketing authorisation that a trial was undertaken to directly compare the clinical effectiveness and safety of ipilimumab at the 3 mg/kg and 10 mg/kg doses; this trial is the ongoing CA184-169 trial.[17] Therefore, based on the evidence presented, the survival benefit may be overestimated in the MS.

The MS presents a mixed treatment comparison and indirect comparisons of ipilimumab, vemurafenib and dabrafenib, however, the ERG does not consider these analyses to be appropriate because of the differences in trial populations between the three included trials. Therefore, there is no reliable data comparing the clinical effectiveness of ipilimumab with vemurafenib in BRAF V600 mutation-positive patients.

In light of the lack of evidence available on the sequencing of treatments for previously untreated malignant melanoma, the ERG does not consider the economic model structure appropriate to address

the decision problem. Although conceptually it is valid to consider the sequencing of treatments, and the ERG recognises that the approval of multiple treatments for advanced melanoma may lead to a sequential use of them in clinical practice, the manufacturer has oversimplified the treatment sequencing approach by using arbitrary assumptions about overall survival on second- and third-line treatments. Furthermore, the ERG has some concerns about the choice of treatment permutations allowed in the model. The manufacturer appears to have presented a partial and incomplete approach to modelling treatment sequences as there are a number of additional treatment permutations that could potentially be applied in clinical practice which the manufacturer has not considered in their analysis.

In the absence of data necessary to model the sequential use of treatments, the manufacturer has modelled second-line OS and PFS by adjusting the corresponding first-line curves downwards by an arbitrary hazard ratio based on data from the previous ipilimumab submission (TA268).[1] The ERG has concerns about the overall approach used for the downward adjustment and with the fact that the same adjustment was applied to vemurafenib despite being based on ipilimumab data. The ERG would have preferred to see the direct use of the OS and PFS curves for second-line treatment with ipilimumab applied in the sequential treatment model as this information was available from TA268, which would have represented a more consistent use of survival data.

For vemurafenib, OS and PFS data were informed from the BRIM-3 trial, which did not have a comparative arm of ipilumumab.[7] As a consequence, separate, independent arms of two different clinical trials were used in the modelling to inform the relative efficacy of ipilimumab with vemurafenib in patients testing positive for the BRAF V600 mutation.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook a range of exploratory analyses to assess the uncertainties raised in the review and critique of the manufacturer's clinical and cost-effectiveness evidence. The ERG's exploratory analyses focused on the issues and uncertainties surrounding the modelling of sequential use of treatments, comparison of overall survival on different doses of ipilimumab (3mg/kg versus 10mg/kg), effects of concomitant DTIC therapy with ipilimumab, relative efficacy estimates for ipilimumab and vemurafenib, costs associated with second-line treatment of ipilimumab, and assumptions regarding health related quality of life (HRQoL) utility values.

The manufacturer's assumptions surrounding the sequencing of treatments had a major impact on the cost-effectiveness results. The manufacturer's base-case ICER for the comparison of ipilimumab with DTIC in the mutation-negative population increased from £16,958 per QALY to between £18,833 and £56,486 per QALY. For the same comparison in the mutation-positive population, the manufacturer's

base-case ICER increased from £31,559 to between £71,335 and £941,091 per QALY. For the comparison with vemurafenib in the mutation-positive population, the ICER of ipilimumab which dominated vemurafenib in the manufacturer's base-case analysis moved to the south-west quadrant of the cost-effectiveness plane resulting in an ICER for vemurafenib of between £27,180 and £84,980. The ERG concluded that the assumptions used by the manufacturer to model the sequencing of treatments were arbitrary and that the only plausible model structure on which to base the estimates of cost-effectiveness was to consider first-line treatments only. The ERG, however, noted that even with the use of a simpler model structure, the estimates of cost-effectiveness remained highly sensitive to the assumptions used to model overall survival on BSC. Assuming that ipilimumab and its comparator treatment moved to the same OS curve upon progression to BSC resulted in an increase in the three-state model ICER of £42,449 to £123,676 per QALY for the comparison of ipilimumab with DTIC. Under this same assumption (i.e. same OS curves for BSC), the three-state model ICER for the comparison of ipilimumab with vemurafenib (£28,980 per QALY) became favourable to vemurafenib such that it dominated ipilimumab.

Superseded – see Erratum

The assumptions surrounding the manufacturer's comparative effectiveness estimates of ipilimumab with DTIC and vemurafenib also had a major impact on the cost-effectiveness results. In order to estimate overall survival for the licensed dose of ipilimumab 3mg/kg, the ERG used a pooled data analysis comparing OS profiles of ipilimumab 3mg/kg (MDX010-20; CA184-022) and 10mg/kg (CA184-007; CA184-008; CA184-022) for a mixed (both previously treated and untreated) patient population, which was presented to the ERG following Points of Clarification to the manufacturer.[14] The ERG estimated an implied hazard ratio for ipilimumab 3mg/kg based on this comparison, which was then used to adjust the overall survival curve for ipilimumab 10mg/kg. Taking the three-state model as the ERG's preferred base-case, the impact of the adjustment on the estimate of cost-effectiveness was significant. For the comparison of ipilimumab with DTIC in the mutation-positive or -negative population, the adjustment for 3mg/kg yielded considerably lower QALYs (2.35 QALYs compared with the base-case of 1.56 QALYs) and resulted in a multi-fold ICER of £331,091 per QALY. A similar analysis was undertaken to assess the impact of concomitant DTIC in the ipilimumab 10mg/kg + DTIC arm of the CA184-024 trial. The effect on the ICER was also remarkable (increased to £674,144 per QALY for the same comparison).

The ERG noted a discrepancy between the acquisition costs of ipilimumab per weekly cycle for first- ([redacted]) and second-line ([redacted]) treatment. The ERG explored the implications of this cost difference on the estimates of cost-effectiveness by allocating equal acquisition costs per cycle ([redacted]) to ipilimumab first- and second-line. For the mutation-negative population, this increased the ICER from the manufacturer's base-case of £16,958 to £25,720 per QALY, while for the mutation-positive population, the ICER for ipilimumab compared with DTIC increased from £31,559

to £40,816 but ipilimumab continued to dominate vemurafenib in the manufacturer's base-case analysis. The ERG also explored the impact of alternatively modelling HRQoL based on pre- and post-progression utility values instead of time-to-death utilities. The resulting impact on the ICER estimates were much more modest compared with the other assumptions discussed above.

2 Background

2.1 Critique of manufacturer's description of underlying health problem.

The description of the underlying health problem in the manufacturer's submission (MS) is appropriate and relevant to the decision problem under consideration.

Malignant melanoma is the 5th most common cancer in the UK, accounting for 4% of all new cancer cases. In 2010 there were 12,818 new cases of malignant melanoma diagnosed in the UK; 6,201 (48%) in men and 6,617 (52%) in women. Malignant melanoma is the 18th most common cause of cancer death in the UK, accounting for 1% of all deaths from cancer. In 2011 there were 2,209 deaths from malignant melanoma in the UK; 1,295 (59%) in men and 914 (41%) in women.[19]

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's overview of current service provision is appropriate and relevant to the decision problem under consideration.

People with unresectable stage III melanoma (where the melanoma has spread to nearby lymph nodes) or stage IV disease (where it has spread to other parts of the body) are usually managed by an oncologist; the mainstay of treatment is systemic therapy. The MS stated that the short life expectancy of patients (around 6-9 months in patients with stage IV disease) means that many patients will only receive first-line therapy, as they do not survive long enough to receive second-line therapy. First-line therapies currently used in the NHS include the chemotherapy dacarbazine (DTIC) or, for patients with BRAF V600 genetic mutation, the BRAF inhibitor vemurafenib (recommended as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma by NICE in December 2012; TA269).[20]

The manufacturer described the limitations of DTIC and vemurafenib; DTIC has not demonstrated an overall survival benefit, and vemurafenib is only effective in patients with BRAF V600 positive disease, which is approximately 50% of melanoma patients. The manufacturer also stated that responses to BRAF inhibitors do not appear to be durable in practice.

Ipilimumab (Yervoy®) is a fully human monoclonal immunoglobulin antibody (IgG1κ) that stimulates the body's own immune system to fight cancer. The MS described the mechanism of action of ipilimumab; known as T-cell mediated immunopotentiation.

In December 2012 ipilimumab was recommended by NICE as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy (TA268).[1] In August 2012, the manufacturer submitted an application to the European Medicines Agency (EMA)

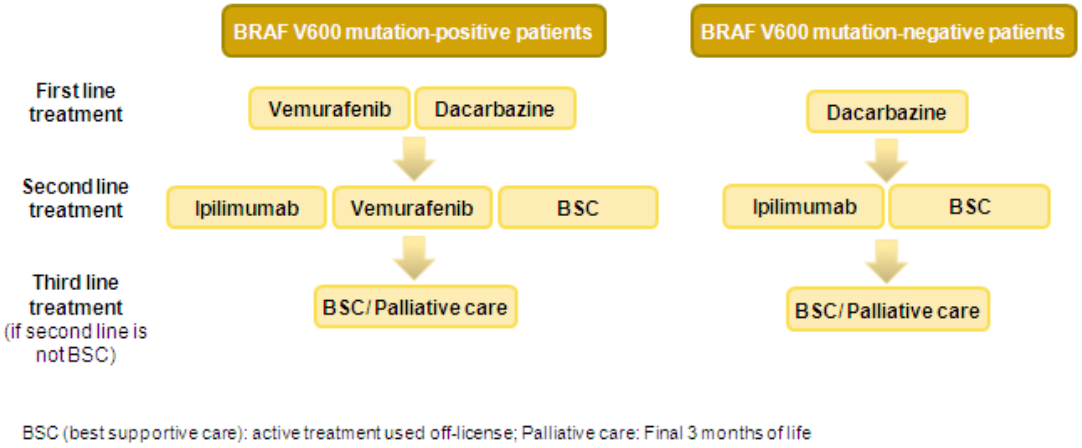
to extend the indication of ipilimumab to previously untreated adult advanced melanoma patients. This was approved in October 2013 and the indication was extended to the treatment of previously untreated adult patients with advanced (unresectable or metastatic) melanoma.[2]

Current NHS practice is that patients with locally advanced or metastatic disease will be tested for BRAF V600 mutation. Patients with a positive test result will receive first-line vemurafenib and then may be offered second-line ipilimumab, although many patients will not be well enough to tolerate this. Patients without BRAF V600 mutation will receive first-line DTIC and then second-line ipilimumab. In patients with BRAF V600 mutation-positive metastatic melanoma there is ongoing debate about the sequencing of treatment; it is unclear if initial therapy with vemurafenib or ipilimumab is preferred, or if there are certain subgroups of patients who will benefit less or more with either treatment. Much of this discussion arises from the USA where both ipilimumab and vemurafenib are licensed for use in both first- and second-line treatment. Until very recently, in the UK, vemurafenib was licensed for first- and second-line treatment, ipilimumab was only licensed for second-line treatment.

There is no randomised evidence to address this sequencing issue, a randomised phase III trial of ipilimumab followed by vemurafenib versus vemurafenib followed by ipilimumab is planned (ECOG E1612).[21] Based on small samples of existing non-randomised data and clinical experience, there is a debate about whether subgroups of BRAF V600 positive patients can be identified who may benefit from ipilimumab treatment prior to vemurafenib. Patients who are relatively stable and well, with low tumour volume, may benefit from being treated with ipilimumab and then switch to vemurafenib, although it is still not clear which patients will demonstrate long-term response. In patients with symptomatic, highly active disease, vemurafenib may be the preferred treatment as such patients may be unlikely to benefit from subsequent ipilimumab.[22-24]

The current clinical pathway of care presented in the MS is shown in Figure 2.1 (Figure 2 in the MS). However, this figure does not include vemurafenib as a third line treatment option for patients with BRAF V600 mutation-positive disease, who received DTIC as first-line therapy and ipilimumab as second-line therapy.

Figure 2.1 Current clinical pathway of care for the treatment of advanced (unresectable or metastatic) melanoma



Footnote: While vemurafenib is both a first- and second-line treatment option, it is highly unlikely that having been used first-line, vemurafenib would subsequentially be used second-line.

The ERG's clinical advisor stated that in current NHS practice the point at which clinicians switch treatment is undefined and left to individual clinicians' discretion. The Summary of Product Characteristics for ipilimumab states that patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response should be conducted only after completion of induction therapy.[3]

3 Critique of manufacturer's definition of decision problem

3.1 Population

The population in the MS matched that specified in the NICE scope, namely "people with previously untreated advanced (unresectable or metastatic) malignant melanoma".

As stated in Section 2.2, in August 2012 the manufacturer submitted an application to the European Medicines Agency (EMA) to extend the indication of ipilimumab to previously untreated adult advanced melanoma patients. This was approved in October 2013 and the indication was extended to the treatment of previously untreated adult patients with advanced (unresectable or metastatic) melanoma.[2] Therefore, the population is appropriate and in line with the marketing authorisation of ipilimumab.

The evidence presented in the MS was derived from clinical trials whose inclusion criteria were adults with previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions, an ECOG performance status of 0 or 1, and most trials stated that patients should have a life expectancy of at least 12 or 16 weeks.[5-8] Patients were excluded if they had brain metastases and some trials excluded patients with a history of prior malignancy. In addition, the clinical trials of vemurafenib and dabrafenib restricted their inclusion criteria to patients with BRAF V600 mutation-positive disease.[7, 8]

In addition to patients represented in the clinical trials, patients seen in practice may have poorer performance status, worse life expectancy, brain metastases or a history of prior malignancy.

3.2 Intervention

The intervention in the MS matched that specified in the NICE scope.

The recommended induction regimen of ipilimumab is 3 mg/kg administered as intravenous infusion over a 90-minute period every three weeks for a total of four doses. However, there is no direct evidence for the effectiveness of ipilimumab monotherapy at a dose of 3 mg/kg compared with DTIC in previously untreated, advanced melanoma patients; the randomised controlled trial (RCT) comparing the clinical effectiveness of ipilimumab with DTIC in previously untreated advanced melanoma patients used ipilimumab at a dose of 10 mg/kg, in combination with DTIC.[5]

It was a condition of the EMA marketing authorisation that a trial was undertaken to directly compare the clinical effectiveness and safety of ipilimumab at the 3 mg/kg and 10 mg/kg doses; this trial is the ongoing CA184-169 trial.[17]

3.3 Comparators

The comparators presented in the manufacturer's decision problem (Table 4 of the MS) matched the NICE scope and were appropriate. However, the MS also included dabrafenib, which has a UK marketing authorisation for monotherapy in the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, and is currently scheduled for a NICE technology appraisal (ID605).[25] Dabrafenib does not currently meet the reference case for comparators, defined as 'therapies routinely used in the NHS, including technologies regarded as current best practice'.

3.4 Outcomes

The outcomes presented in the manufacturer's decision problem (Table 4 of the MS) matched the NICE scope and were appropriate.

The manufacturer argues that overall survival is a more clinically relevant endpoint than progression-free survival, because of the mechanism of action of ipilimumab. With ipilimumab, because the tumour is "stimulated" immunologically, it may get larger for a short period of time, due to an influx of inflammatory cells, after which it begins to shrink. Thus, in conventional clinical trial assessment terms, the patient appears to have progressed. However, the tumour is actually responding to ipilimumab therapy. Patients on ipilimumab therapy who ultimately achieve a positive clinical outcome may appear to have progressed when assessed in the early stages of treatment, therefore, the manufacturer argues that progression-free survival is not an accurate measure of the eventual response to ipilimumab.

4 Clinical Effectiveness

This section contains a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results. The ERG's conclusions on the clinical effectiveness of ipilimumab for the treatment of previously untreated advanced malignant melanoma are presented at the end of this section.

4.1 Critique of the methods of review(s)

The MS described a systematic review evaluating the clinical efficacy and tolerability of ipilimumab and comparator therapies for the treatment of adult patients with previously untreated advanced malignant melanoma. No direct evidence was identified which evaluated the effectiveness of ipilimumab monotherapy, at its licensed dose of 3 mg/kg, compared with DTIC, vemurafenib or dabrafenib for the treatment of previously untreated, advanced melanoma patients. The evidence presented in the MS comprised of four RCTs identified in the systematic review, along with additional non-RCT evidence selected by the manufacturer.

Superseded – see Erratum

4.1.1 Search strategy

The MS described the systematic review search strategies used to identify relevant clinical effectiveness studies on the use of ipilimumab and comparator therapies for the treatment of adult patients with previously untreated advanced malignant melanoma. The search strategies were described in the main body of the submission, and full details were provided in the Appendices.

The electronic databases MEDLINE, MEDLINE In Process, EMBASE, the Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Health Technology Assessment Database and the Database of Abstracts of Reviews of Effects (DARE)), CINAHL and ClinicalTrials.gov were searched in May 2013. In addition, the 2009 to 2012 conference proceedings of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the Society for Melanoma Research (SMR) were searched on 9th May 2013. The manufacturer attempted to search the conference proceedings of the European Association of Dermato-Oncologists (EADO) and Perspectives in Melanoma (PiM), however the abstracts could not be accessed so were not searched. The reference lists of previous systematic reviews and clinical guidelines identified were hand searched to identify any additional relevant studies, and unpublished data from Bristol-Myers Squibb were reviewed for relevance to the research question. Search strategies used for each database were documented in Appendix 2, Section 10.2.4 of the MS.

Searches were limited to studies published between 1970 and May 2013, with the justification that the earliest melanoma trial was published in 1972. In view of the therapies eligible for inclusion in the review, this was appropriate. The searches were not limited by language.

In Appendix 6 (Section 10.6), under 'Search strategy for Section 6.8 (Non-RCT evidence)', the MS states "Not applicable" for each of the subsections; however, non-RCT evidence was included in the review. Therefore, it is unclear in the MS how these studies were identified. The ERG asked the manufacturer to clarify how non-RCT evidence was identified; the manufacturer responded that non-RCT evidence was not searched for systematically.

Generally, the search strategies were well reported in the MS. The exact strategies used along with the databases searched, the database service provider, dates of searches and date span of the searches are all clearly reported. Searches for both published and unpublished literature were carried out and all of the NICE specified databases were searched.

The textword and subject headings used in the search strategies for ipilimumab and the comparator drugs were appropriate. Various synonyms and spelling variations for melanoma or skin cancer have been included in the strategy. However the terms neoplas$ and tumor$ have not been included. Boolean operators, truncation and field searches have been used appropriately.

Superseded – see

The search strategies were limited to RCTs or systematic reviews using study design filters developed by SIGN. The SIGN filters have been developed in-house and have not been independently validated. Other validated search filters with high sensitivity are freely available and could have been used. A further issue with restricting the clinical effectiveness searches to RCTs or systematic reviews is that adverse events data from other study types may not have been identified.

Erratum

Unpublished literature was sought from Clinicaltrials.gov using an appropriate search strategy. In addition, several conference proceedings were searched; however details of how they were searched were not reported.

Although minor issues have been raised with the search strategies for clinical effectiveness, it is unlikely that any relevant RCTs have been missed. Non-RCT evidence was not searched for systematically; therefore, other studies may have been missed.

4.1.2 Inclusion criteria

Studies had to have at least an abstract reported in English to be screened for inclusion in the review. No details of the study selection process were described in the MS; therefore, it is unclear whether appropriate methods were used to reduce the potential for reviewer bias and error.

The inclusion criteria relating to the population of interest appear to have been appropriate and in line with both the decision problem and the marketing authorisation of ipilimumab. The inclusion criteria relating to outcomes of interest appear to have been appropriate, and included all those specified in the scope.

As discussed in Section 3.3, it is unclear why dabrafenib was added to the inclusion criteria relating to interventions of interest, as this was not presented in Table 4 of the MS, which presented the decision problem addressed in the submission. The manufacturer stated that it was included as a clinical comparator, as it is licensed for monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, and is currently scheduled for a NICE technology appraisal. However, it does not meet the reference case for comparators, defined as "therapies routinely used in the NHS, including technologies regarded as current best practice".

Prospective non-RCTs and observational studies were listed under 'exclusion criteria' for the review of the clinical effectiveness data; however, two ongoing retrospective observational studies and a pooled analysis of a subgroup of patients included in four RCTs were included in the MS, due to the lack of RCT evidence directly investigating ipilimumab 3 mg/kg monotherapy in untreated patients. Non-RCT evidence was not searched for systematically (see Section 4.1.1), therefore, other relevant studies may have been missed and this selected data may not be representative of the full non-RCT evidence base.

Superseded – see Erratum

A flow chart of the study selection process was presented in the MS (Figure 5), which stated that six original RCTs were included in a quantitative synthesis. An additional record of an ongoing trial was included in the qualitative synthesis, along with 9 kin publications, related to the six included RCTs. The complete list of relevant RCTs was as follows:

- CA184-024[5]
- MDX010-08[6]
- CA184-004[13]
- CA184-022[12]
- CA184-169[17]
- BREAK-3[8]
- BRIM-3[7]

However, CA184-169[17], CA184-004[13] and CA184-022[12] were then excluded as CA184-169[17] is an ongoing study with no preliminary results available. CA184-004[13] and CA184-022[12] included both pre-treated and treatment-naïve patients, but preliminary survival analysis conducted on the chemotherapy-naïve subgroups of these trials was deemed inappropriate for use, due to the low patient numbers in each treatment arm that met the criteria for inclusion in the review. Therefore, these three trials were excluded from the review, and four trials were included in the systematic review; CA184-024,[5] MDX010-08,[6] BREAK-3[8] and BRIM-3.[7]

The ERG searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, the EU Clinical Trials Register and the WHO Trials Registry and did not identify any additional RCTs that should have been included in the review.

4.1.3 Data extraction

Two reviewers independently extracted data from the included trials into a pre-defined data extraction table designed in Microsoft Access®, reducing the potential for error or bias. In case of disagreement between the two reviewers, a third reviewer would have extracted data with final results attained by consensus, however, this was not necessary.

Adequate data from the four included RCTs were presented in the MS.

It is unclear how data from the included observational studies were extracted, as no details were provided in the MS for non-RCT evidence (see MS Appendix 6, Section 10.6.7).

4.1.4 Quality assessment

A table of the quality assessment results for the four included RCTs was presented in the MS (Table 15), which included the quality criteria specified by NICE. In addition, further details were presented in Appendix 3; although there were some minor inconsistencies between the quality assessment results presented in Table 15 and those presented in Appendix 3, relating to the adequacy of concealment of treatment allocation for the open label trials (which was coded as 'adequate' or 'unclear' in Table 15, but 'not applicable' in Appendix 3).

Quality assessment results were checked by the ERG. However, the ERG was unable to find details of the methods of randomisation for the MDX010-08[6] and BRIM-3[7] trials within the study reports. The MS stated that these were undertaken using a centralised randomisation scheme.

The quality of the included non-RCT evidence was presented in Appendix 7. The manufacturer acknowledged the potential biases introduced through the use of retrospective observational data and pooled analyses.

4.1.5 Evidence synthesis

The manufacturer described the results of the individual trials separately, which was appropriate in view of the differences in study design, participant and intervention characteristics.

A mixed treatment comparison of ipilimumab (10 mg/kg plus DTIC), and the BRAF inhibitors vemurafenib and dabrafenib was presented, using the CA184-024, BRIM-3 and BREAK-3 trials, with DTIC being the common comparator treatment in each of the trials.[5, 7, 8] Indirect pairwise

comparisons, determined using the Bucher method, were also presented. The ERG does not consider these analyses to be appropriate because of differences in patients' baseline characteristics between the ipilimumab, vemurafenib and dabrafenib trials, resulting in patients in the vemurafenib and dabrafenib trials having a worse prognosis than patients in the ipilimumab trial (differences in the proportion of patients with elevated serum lactate dehydrogenase levels and M1c disease).

4.1.6 Conclusions from critique of systematic review methods

The search strategy for RCT evidence was appropriate, comprehensive and well documented. The inclusion criteria for the population and outcomes of interest were appropriate, but it is not clear why dabrafenib was included as an intervention of interest, since it was not included in the decision problem and is not currently routinely used in the NHS. The evidence on dabrafenib does not inform the clinical effectiveness of ipilimumab or vemurafenib and the comparison between ipilimumab and dabrafenib is not used in the economic model. The review included data from observational studies, despite this study design being listed under 'exclusion criteria' for the review; in addition, there was no systematic search for the included non-RCT evidence.

Superseded – see Erratum

The methods used for study selection were not reported; therefore it is unclear whether they were susceptible to error or bias. Two of the studies which were stated as being included in the quantitative synthesis were excluded from the review due to the low patient numbers in each treatment arm that met the criteria for inclusion in the review. No relevant RCTs of ipilimumab and comparator therapies for the treatment of adult patients with previously untreated advanced malignant melanoma appear to have been overlooked. Adequate details of the included studies were presented and quality assessment was appropriate. Additional evidence was presented in the MS from trials that were excluded from the review; CA184-004, CA184-022 and MDX010-020.[12, 13, 18]

Indirect comparisons comparing ipilimumab (10 mg/kg plus DTIC), with the BRAF inhibitors vemurafenib and dabrafenib were presented, however the ERG does not consider these indirect comparisons to be appropriate because of differences in patients' baseline characteristics between the three included trials.

4.1.7 Ongoing studies

The MS described an ongoing dose-comparison trial requested by the FDA and the EMA comparing the clinical effectiveness and safety of two doses of ipilimumab; 3 mg/kg versus 10 mg/kg (CA184-169).[17] The trial is not due for completion before December 2016, and no preliminary results were available at the time of this appraisal.

The MS also stated that additional efficacy, safety and survival data from two ongoing, retrospective observational studies (CA184-332[9] and CA184-338[10]) are expected within the next three months; interim analyses from these two observational studies were presented in the section of the MS on non-RCT evidence. Data from a follow-up study (CA184-025)[26] of patients previously enrolled in CA184-004[13] and CA184-022[12] may also become available within the next 12 months.

The MS also stated that data from other ongoing ipilimumab studies may become available in the next 12 months, but that these were not highlighted in the MS because they use different doses of ipilimumab and other drug combinations to those in the submission. The ERG identified several ongoing trials (phase I, II and III) of ipilimumab, assessing its use in combination with other types of therapy, such as the kinase inhibitors vemurafenib, trametinib and dabrafenib and the immunotherapies interferon alfa-2b, nivolumab and talimogene laherparepvec; but no additional ongoing RCTs that were of direct relevance to the decision problem addressed in the MS.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Trials included in the review

There was no direct evidence for the clinical effectiveness of ipilimumab 3mg/kg monotherapy compared with DTIC, vemurafenib or dabrafenib for the treatment of previously untreated, advanced melanoma patients.

The RCT evidence presented in the MS included:

- a large double-blind RCT of ipilimumab 10 mg/kg plus DTIC (including a maintenance phase of ipilimumab therapy) compared with DTIC plus placebo for the treatment of previously untreated, advanced melanoma patients (CA184-024);[5]
- a small open-label RCT of ipilimumab 3 mg/kg plus DTIC compared with ipilimumab alone for the treatment of chemotherapy-naïve metastatic melanoma patients (MDX010-08);[6]
- a large RCT of vemurafenib compared with DTIC for the treatment of previously untreated, BRAF V600 mutation positive advanced melanoma patients (BRIM-3);[7]
- a reasonably large RCT of dabrafenib compared with DTIC for the treatment of BRAF V600 mutation positive advanced melanoma patients who had not received previous antitumour therapy (other than interleukin-2) (BREAK-3).[8]

The MS also described the following non-RCT evidence:

a) interim results from two ongoing retrospective observational studies of ipilimumab 3 mg/kg for the treatment of previously untreated, advanced melanoma patients (CA184-332 and CA184-338);[9, 10]
b) a pooled analysis of treatment-naïve or chemotherapy-naïve advanced melanoma patients who were included in four RCTs (MDX010-08, CA184-004, CA184-022 and MDX010-020).[11]

In addition, two very small subgroup assessments of chemotherapy-naïve patients included in two RCTs comparing ipilimumab 3 mg/kg with ipilimumab 10 mg/kg (CA184-004[13] and CA184-022[12]) were described. However, these data were deemed inappropriate to include in the MS, due to the low patient numbers in each treatment arm. A treatment-naïve subgroup assessment of an ongoing RCT comparing ipilimumab 3 mg/kg with ipilimumab 10 mg/kg for the treatment of patients with advanced melanoma was also described (CA184-169),[17] although no results were available at the time of the appraisal, therefore, the MS states that it was not considered further.

The MS refers to the clinical equivalence of ipilimumab at a dose of 3 mg/kg and 10 mg/kg and cites the trials CA184-004[13] and CA184-022,[12] including both previously treated and untreated patients, as the source of the evidence, despite these full trials not meeting the inclusion criteria for the review. In response to the ERG's points for clarification document, the manufacturer also reported the results of a pooled data analysis that was submitted for the STA "ipilimumab in previously treated unresectable malignant melanoma" (TA268),[1] which compared overall survival profiles of ipilimumab 3 mg/kg (MDX010-20 and CA184-022) and 10 mg/kg (CA184-007, CA184-008 and CA184-022) for a mixed population of both previously treated and untreated patients.[14]

Another trial, MDX010-020,[18] which compared the clinical effectiveness of ipilimumab 3 mg/kg plus placebo versus ipilimumab 3 mg/kg plus gp100 versus gp100 plus placebo in previously-treated melanoma patients did not meet the inclusion criteria for the review, however, this trial is also referred to in the MS.

4.2.1.1 RCT evidence

The study design, eligibility criteria and participant baseline characteristics of the four included RCTs are summarised in Tables 4.1, 4.2 and 4.3, respectively (Tables 10, 11 and 12 of the MS).

Table 4.1 Comparative summary of methodology of the RCTs

	CA184-024[5]	MDX010-08[6]	BREAK-3[8]	BRIM-3[7]
Location	111 sites in Africa, Australia, Europe, North America and South America.	12 sites in the US.	70 sites in 12 countries worldwide.	104 centres in 12 countries worldwide.
Design	Multinational, randomised, double-blind, phase III study designed to assess if ipilimumab addition to standard therapy (DTIC) improves overall survival in patients with previously untreated metastatic melanoma.	Multicentre, randomised, open-label, phase II, cross-over study designed to evaluate the efficacy and safety of ipilimumab addition to standard therapy (DTIC) in patients with chemotherapy-naïve metastatic melanoma.	Multinational, randomised, open-label, phase III, cross-over study designed to compare dabrafenib to standard therapy (DTIC) in patients with previously untreated metastatic melanoma with the BRAF V600 mutation.	Multinational, randomised, phase III, cross-over study designed to assess if vemurafenib prolongs survival in comparison to standard therapy (DTIC) in patients with previously untreated metastatic melanoma with the BRAF V600 mutation.
Method of randomisation	A centralised randomisation scheme was used to assign subjects in a 1:1 ratio. Randomisation was stratified according to baseline M stage; ECOG performance status; and study site.	A centralised randomisation scheme was used to assign subjects in a 1:1 ratio. Randomisation was stratified using a random block size of 2 or 4.	A centralised, computerised, interactive voice activated response randomisation scheme was used to assign subjects in a 3:1 ratio. Randomisation was stratified according to baseline M stage.	Randomisation was used to assign subjects in a 1:1 ratio. Randomisation was stratified according to baseline M stage; ECOG performance status; geographic region; and serum lactate dehydrogenase.
Method of blinding	Patient; care provider; outcome assessor on site	Open-label study: treatment was not blinded	Not reported.	Independent review committee only.
Intervention **Comparator**	Ipilimumab 10mg/kg + DTIC 850mg/m^2 (n=250) DTIC 850mg/m^2 (n=252)	Ipilimumab 3mg/kg + DTIC 1000mg/m^2 (n=36) Ipilimumab 3mg/kg (n=40)	Dabrafenib (n=187) DTIC 1000mg/m^2 (n=63)	Vemurafenib 960mg (n=337) DTIC 1000mg/m2 (n=338)
Treatment schedule	Induction phase: treatment on weeks 1, 4, 7 and 10; DTIC only on weeks 13, 16, 19 and 22 Maintenance phase: ipilimumab or placebo every 12 weeks (responsive patients only)	Ipilimumab (both groups): weeks 1, 5, 9 and 13 DTIC: weeks 1, 4, 7, 10, 13 and 16	Dabrafenib: twice daily DTIC: every 3 weeks	Vemurafenib: twice daily DTIC: every 3 weeks
Primary outcomes	Overall survival	Objective response rate (CR +	Progression-free survival	Overall survival

	CA184-024[5]	MDX010-08[6]	BREAK-3[8]	BRIM-3[7]
		PR)* Safety *RECIST assessments performed every 4 weeks after criteria for response were first met	(investigator assessed)	Progression-free survival
Secondary outcomes	Progression-free survival Overall response rate (CR + PR)* Disease control rate (CR + PR + SD)* Time to response Duration of response Safety HRQL: (EORTC) QLQ-C30 at baseline and weeks 4, 7, 12, 24, 36, 48 *RECIST assessments performed at week 12 and in responsive patients at weeks 16, 20 and 24 and every 6 weeks through week 48. Then every 12 weeks.	Duration of response Stable disease rate* Survival Lymphocyte subpopulations Pharmacokinetics *RECIST assessments performed every 4 weeks after criteria for response were first met	Progression-free survival (IRC assessed) Overall survival Objective response rate (CR + PR)* Progression-free survival post cross-over Duration of response HRQL Safety and tolerability Support of a BRAF mutation assay validation *RECIST assessments performed at weeks 6 and 12 and every 9 weeks thereafter	Confirmed response rate (CR + PR)* Time to response Duration of response Number of participants with AEs *RECIST assessments performed at weeks 6 and 12 and every 9 weeks thereafter
Duration of follow-up	37 months post last patient enrolment	Median, months: Ipilimumab + DTIC: 20.9 Ipilimumab: 16.4	Median, months: Dabrafenib: 5.0	*Initial analysis* Median, months: Vemurafenib: 3.8 DTIC: 2.3 *Extended analysis* Median, months: Vemurafenib: 10.5 DTIC: 8.4

AEs, adverse events; CR, complete response; DTIC, dacarbazine; ECOG, Eastern Cooperative Oncology Group; HRQL, health-related quality of life; IRC, independent review committee; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours ;SD, stable disease; US, United States

Table 4.2 Eligibility criteria in CA184-024, MDX010-08, BREAK-3 and BRIM-3

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
CA184-024[5]	≥18 years of age; previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions; an ECOG performance status of 0 or 1; a life expectancy of ≥16 weeks.	Prior treatment for metastatic disease; evidence of brain metastasis (as confirmed on imaging); primary ocular or mucosal melanoma; autoimmune disease; concomitant treatment with immunosuppressive agents or long-term use of systemic glucocorticoids (except for the management of AEs during the course of the study) was not allowed.
MDX010-08[6]	≥18 years of age; histologic diagnosis of unresectable metastatic melanoma; progressive disease defined by Response Evaluation Criteria in Solid Tumours (RECIST); ≥1 measurable lesion; life expectancy ≥12 weeks; discontinued any other melanoma therapy ≥4 weeks before enrolment.	Any other prior malignancy; history or clinical evidence of autoimmune disease; treatment with an immunosuppressive drug, melanoma vaccine, anti-CTLA-4 antibody, or chemotherapy within the past 5 years (except for regional chemotherapy); active infection requiring therapy; chronic active hepatitis B or C virus infection, or human immunodeficiency virus reactivity.
BREAK-3[8]	Histologically confirmed, measurable metastatic melanoma (stage IV or unresectable stage III) with BRAF V600 mutation by central testing using an investigational-use-only assay; 18 years of age or older; ECOG performance status of 0 or 1; adequate haematological, hepatic, renal, and cardiac function.	Previous anti-tumour therapy for unresectable or metastatic melanoma other than interleukin 2; surgery, radiotherapy, or immunotherapy within 4 weeks; history of HIV infection; glucose-6-dehydrogenase deficiency; previous malignancy within the past 5 years; CNS metastases unless patients were without evidence of active CNS metastases for more than 3 months after surgery or stereotactic radiosurgery; corrected QT interval of 480 ms or more; acute coronary syndrome, coronary angioplasty, placement of stents, or cardiac arrhythmia (other than sinus arrhythmias) within the previous 24 weeks; abnormal cardiac valve morphology grade 2 or higher on ECHO cardiography; known cardiac metastases.
BRIM-3[7]	Unresectable, previously untreated stage IIIC or stage IV melanoma that tested positive for the BRAF V600 mutation on real-time polymerase-chain-reaction assay; ≥18 years of age; life expectancy of ≥3 months; ECOG performance status of 0-1; adequate hematologic, hepatic, and renal functions.	History of cancer within the past 5 years (except for basal- or squamous-cell carcinoma of the skin or carcinoma of the cervix) or metastases to the central nervous system, unless such metastases had been definitively treated more than 3 months previously with no progression and no requirement for continued glucocorticoid therapy; concomitant use of any other anticancer therapy was not allowed.

AEs, adverse events; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HIV, Human immunodeficiency virus
Source: Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 4.3 Baseline characteristics of participants in CA184-024, MDX010-08, BREAK-3 and BRIM-3 across randomised groups

	CA184-024[5]		MDX010-08[6]		BREAK-3[8]		BRIM-3[7]	
	Ipi + DTIC (n=250)	DTIC (n=252)	Ipi + DTIC (n=35)	Ipi (n=37)	Dab (n=187)	DTIC (n=63)	Vem (n=337)	DTIC (n=338)
Age, median years (range)	57.5*	56.4*	60 (27-82)	66 (25-82)	53 (22-93)	50 (21-82)	56 (21-86)	52 (17-86)
Male, n (%)	152 (60.8)	149 (59.1)	26 (74.3)	21 (56.8)	112 (59.9)	37 (58.7)	200 (59.4)	181 (53.6)
White, n (%)	249 (99.6)	251 (99.6)	31 (88.6)	34 (91.9)	187 (100)	63 (100)	333 (98.8)	338 (100)
ECOG performance status, n (%)	0 = 177 (70.8) 1 = 73 (29.2)	0 = 179 (71.0) 1 = 73 (29.0)	NR	NR	0 = 124 (66.3) ≥1 = 62 (33.2)	0 = 44 (69.8) ≥1 = 16 (25.4)	0 = 229 (68.0) 1 = 108 (32.0)	0 = 230 (68.0) 1 = 108 (32.0)
Metastasis stage, n (%)	M0 = 6 (2.4) M1a = 37 (14.8) M1b = 64 (25.6) M1c = 143 (57.2)	M0 = 8 (3.2) M1a = 43 (17.1) M1b = 62 (24.6) M1c = 139 (55.2)	M1a = 6 (17.1) M1b = 12 (34.3) M1c = 16 (45.7)	M1a = 8 (21.6) M1b = 8 (21.6) M1c = 21 (56.8)	M0 = 6 (3.2) M1a = 23 (12.3) M1b = 34 (18.2) M1c = 124 (66.3)	M0 = 1 (1.6) M1a = 10 (15.9) M1b = 12 (19.0) M1c = 40 (63.5)	M0 = 20 (5.9) M1a = 34 (10.1) M1b = 62 (18.4) M1c = 221 (65.6)	M0 = 13 (3.8) M1a = 40 (11.8) M1b = 65 (19.2) M1c = 220 (65.1)
Duration of melanoma, months	36.6	40.4	23.2	46.3	NR	NR	NR	NR
Lactate dehydrogenase, n (%)	≤ULN = 157 (62.8) >ULN = 93 (37.2)	≤ULN = 140 (55.6) >ULN = 110 (43.7)	≤ULN = 27 (77.1) >ULN = 8 (22.9)	≤ULN = 27 (73.0) >ULN = 10 (27.0)	≤ULN = 119 (63.6) >ULN = 67 (35.8)	≤ULN = 43 (68.3) >ULN = 19 (30.2)	≤ULN = 142 (42.1) >ULN = 195 (57.9)	≤ULN = 142 (42.0) >ULN = 196 (58.0)

DTIC, dacarbazine; NR, not reported; ULN, upper limit of normal; UR, unresectable

As shown in Table 4.1, the large double-blind CA184-024 trial is the only trial that compared ipilimumab with DTIC.[5] However, the dose of ipilimumab used in this trial was 10 mg/kg (with maintenance therapy), in combination with DTIC. Therefore, it does not provide direct evidence for the clinical effectiveness of ipilimumab monotherapy at a dose of 3 mg/kg every three weeks for a total of four doses, which is the licensed dose.

The small open-label MDX010-08 phase II trial compared ipilimumab (3 mg/kg) monotherapy with ipilimumab (3 mg/kg) in combination with DTIC.[6] The treatment schedule for ipilimumab therapy used in this trial also differed from the licensed schedule, as patients were treated every four weeks for a total of four doses, rather than every three weeks, as per the license.

The reasonably large open-label BREAK-3 trial compared dabrafenib with DTIC in patients that tested positive for the BRAF V600 mutation.[8]

The large open-label BRIM-3 trial compared vemurafenib with DTIC in patients that tested positive for the BRAF V600 mutation.[7]

The dosing schedule of DTIC was similar between the four trials and reflected doses used in clinical practice (850 to 1250 mg/m^2).

The participant inclusion and exclusion criteria of the four trials were similar, except that the BREAK-3 and BRIM-3 trials only included patients that tested positive for the BRAF V600 mutation. Both dabrafenib and vemurafenib target the BRAF pathway; therefore, have no effect in BRAF V600 mutation-negative patients. Whilst the manufacturer argues that the clinical activity of ipilimumab is not affected by BRAF V600 status, BRAF mutation has been associated with an increased risk of mortality in melanoma patients.[27]

The treatment history of patients eligible for inclusion in the trials also differed slightly in that the CA184-024 and BRIM-3 trials did not allow any prior anti-tumour therapy, whilst in the BREAK-3 trial patients who had received prior immunotherapy with interleukin-2 were also eligible for inclusion, and in the MDX010-08 trial chemotherapy-naïve patients who had received prior immunotherapy, melanoma vaccine or anti-CTLA-4 antibody more than 5 years previously were eligible for inclusion.

The MS stated that the baseline characteristics of the participants were generally similar between the four RCTs, however, the proportion of patients who had elevated levels of lactate dehydrogenase (a known prognostic factor) differed between trials, as shown in Table 4.3; indicating that patients in the BRIM-3 trial had a worse prognosis than those in the other three trials. In addition, the proportion of

patients with stage M1c disease was also slightly higher in the BREAK-3 and BRIM-3 trials than the CA184-024 and MDX010-08 ipilimumab trials. Time from initial diagnosis of melanoma to first dose of study therapy was not reported in the BREAK-3 and BRIM-3 trials, so cannot be compared.

The primary outcome of interest in the CA184-024 and BRIM-3 trials was overall survival. In the BREAK-3 trial the primary outcome was progression-free survival, and in the MDX010-08 trial it was objective response rate. The MDX010-08 trial was underpowered to detect a statistically significant difference in overall survival between treatment groups.

The manufacturer argues that overall survival is a more clinically relevant endpoint than progression-free survival; because of the mechanism of action of ipilimumab progression-free survival is not an accurate measure of the eventual response to ipilimumab, see Section 3.4.

The outcomes defined in the final scope issued by NICE were overall survival, adverse effects of treatment and health related quality of life.[4] All of these outcomes were assessed in the CA184-024 ipilimumab trial, using appropriate criteria.[5] Pre-planned subgroup analyses were conducted in the CA184-024 trial based on the following participant characteristics: M-stage, baseline LDH, age, female age, ECOG status, prior adjuvant therapy, race and gender.

The MS also referred to trials CA184-004 and CA184-022, despite these full trials not meeting the inclusion criteria for the review. The CA184-004 trial was a small double-blind randomised phase II trial designed to explore the association between tumour microenvironment biomarkers and clinical activity of ipilimumab.[13] The trial included 20 treatment-naïve advanced melanoma patients and 62 previously treated patients; 40 patients received ipilimumab at a dose of 3 mg/kg and 42 patients received ipilimumab at a dose of 10 mg/kg. The CA184-022 trial was a double-blind randomised dose-ranging phase II trial.[12] The trial included 217 patients who had received at least one previous treatment with an antitumour regimen; 72 patients received ipilimumab at a dose of 0.3 mg/kg, 72 patients received ipilimumab at a dose of 3 mg/kg and 73 patients received ipilimumab at a dose of 10 mg/kg.

4.2.1.2 Non-RCT evidence

The non-RCT evidence included interim results from two ongoing retrospective observational studies of ipilimumab 3 mg/kg for the treatment of previously untreated, advanced melanoma patients; both studies included patients treated in the US between April 2011 and September 2012, therefore it is unclear whether the same patients were included in both retrospective observational studies (CA184-332 and CA184-338).[9, 10] The MS also presented a pooled analysis of treatment-naïve or chemotherapy-naïve advanced melanoma patients who were randomised to ipilimumab 3 mg/kg

monotherapy treatment arms of four RCTs (MDX010-08, CA184-004, CA184-022 and MDX010-020).[11] Since the MDX010-08 trial was also included in the MS separately, there is some double-counting of patients between the results presented for the MDX010-08 trial and the pooled chemotherapy-naïve dataset, which had a total of 78 patients.

The study design and participant baseline characteristics for the three included non-RCT studies are presented in Table 4.4 (Tables 22 and 24 of the MS). The dosing schedule of ipilimumab was the same in the three non-RCTs and reflected the license. There were some clinically significant differences in the baseline characteristics of patients between the three datasets; including differences in performance status, disease stage, presence of brain metastases, duration of melanoma and prior immunotherapy, as shown in Table 4.4. Each of the non-RCTs assessed overall survival as an outcome.

The manufacturer compared the results of these uncontrolled studies with the DTIC arm of the CA184-024 trial, which is inappropriate, because of the differences in study design and patient characteristics.

Superseded – see Erratum

Table 4.4 Study design and participant baseline characteristics of the non-RCTs

	CA184-332[9]	CA184-338[10]	Pooled chemotherapy-naïve dataset (from clinical trials)[11]
Location	Multiple US oncology sites.	27 sites in the US.	Multiple sites in multiple countries worldwide.
Design	Multi-site, observational, retrospective medical chart review of patient medical records, designed to understand how ipilimumab is being used in treatment-naïve unresectable or metastatic melanoma patients in routine clinical practice.	Multi-site, observational, retrospective medical chart review of patient medical records, designed to understand how ipilimumab is being used in treatment-naïve unresectable or metastatic melanoma patients in routine clinical practice.	Pooled analysis of patients randomised to ipilimumab 3mg/kg monotherapy treatment arms of three phase II trials: MDX010-08; CA184-004; CA184-022 and one phase III trial: MDX010-20 designed to further assess the survival profile of ipilimumab in previously untreated subjects.
Intervention	Ipilimumab 3mg/kg	Ipilimumab 3mg/kg	Ipilimumab 3mg/kg
Treatment schedule	Every 3 weeks for a total of 4 doses	Every 3 weeks for a total of 4 doses	Induction phase: weeks 1, 4, 7 and 10 Maintenance phase: every 12 weeks (responsive patients only from CA184-004; CA184-022) Re-induction phase: every 3 weeks (stable disease patients only from MDX010-20).
Primary outcomes	Demographic & clinical characteristics Occurrence & severity of AEs and TEAEs Patterns of care Overall survival	Demographic & clinical characteristics Occurrence & severity of AEs and TEAEs Patterns of care Overall survival	Overall survival
Secondary outcomes	Healthcare resource use	Healthcare resource use	-
Duration of follow-up	Interim analysis Median, months: 8.5	Interim analysis Median, months: 12.0	Median, months: 11.6 2 year survival rate: 32%
Sample size, n	61	120	78
Age, mean years	64	61.3	57.4
Male, n (%)	40 (65.6)	79 (65.8)	47 (60.3)
ECOG performance status, n (%)	0 = 39 (63.9) 1 = 16 (26.2) >1 = 3 (4.9)	0 = 49 (40.8) 1 = 62 (51.7) >1 = 7 (5.8)	0 = 45 (57.7) 1 = 30 (38.5) >1 = 3 (3.8)
Metastasis stage, n (%)	M0 = 0 M1a = 20 (29.5) M1b = 23 (37.7) M1c = 18 (29.5)	M0 = 14 (11.7) M1a = 13 (10.8) M1b = 27 (22.5) M1c = 66 (55.0)	M0 = 0 M1a = 18 (23.1) M1b = 16 (20.5) M1c = 44 (55.6)
Brain metastasis, n (%)	20 (32.8)	9 (7.5)	0
Duration of melanoma, median months	10.3	12.9	39.0

	CA184-332[9]	CA184-338[10]	Pooled chemotherapy-naïve dataset (from clinical trials)[11]
Lactate dehydrogenase, n (%)	≤ULN = 27 (44.3) >ULN = 18 (32.8)	≤ULN = 67 (55.8) >ULN = 44 (36.7)	≤ULN = 56 (71.8) >ULN = 21 (26.9)
BRAF V600 mutation, n (%)	Negative = 31 (50.8) Positive = 8 (31.1)	Negative = 76 (63.3) Positive = 21 (17.5)	NR
Prior immunotherapy, n (%)	0	16 (13.3)	41 (52.6)

ULN = upper limit of normal; NA = not applicable; NR = not reported

In addition, the manufacturer presented the results of an additional pooled analysis in their response to the ERG's points for clarification document, regarding the comparison of ipilimumab 3 mg/kg with 10 mg/kg doses.[14] The pooled analysis compared overall survival profiles of ipilimumab 3 mg/kg (MDX010-20 and CA184-022) and 10 mg/kg (CA184-007, CA184-008 and CA184-022) for a mixed population of both previously treated and untreated patients. However, no methods for the pooled analysis or details of the included studies were presented. Therefore, it is not possible to determine the reliability of the results of the pooled analysis or the generalisability of results to previously untreated patients eligible for ipilimumab first-line therapy; particularly since this pooled analysis was primarily in previously treated patients.

4.2.2 Summary of the quality of the included trials

4.2.2.1 RCT evidence

Results of the quality assessment were presented in Table 15 of the MS.

The CA184-024 trial was a large well-conducted, double-blind RCT; randomisation and concealment of treatment allocation were adequate, the treatment groups were generally similar at baseline (although slightly more patients in the DTIC treatment group had elevated levels of lactate dehydrogenase), follow-up was adequate, an appropriate intention-to-treat analysis was performed and there were no unexpected imbalances in drop-outs between treatment groups.[5] However, the health related quality of life data were limited, with only around two thirds of the surviving trial participants completing the EORTC QLQ-C30 assessment at week 12, and fewer completing assessments at weeks 24, 36 and 48. The ERG asked the manufacturer to provide further information on the reasons for non-completion of the EORTC QLQ-C30 questionnaire, but the manufacturer stated that these data were not available.

The MDX010-08 trial was a small open-label phase II trial, underpowered to detect a statistically significant difference in overall survival.[6] It is unclear whether randomisation was carried out appropriately, the treatment groups were generally similar at baseline (although the time from initial

pathological diagnosis of melanoma to first dose of study therapy was twice as long in the ipilimumab monotherapy group), follow-up was adequate, an appropriate intention-to-treat analysis was performed and there were no unexpected imbalances in drop-outs between treatment groups.

The BREAK-3 trial was a reasonably large open-label RCT; randomisation appears to have been carried out appropriately, the treatment groups were generally similar at baseline, an appropriate intention-to-treat analysis was performed and there were no unexpected imbalances in drop-outs between treatment groups.[8] However, median follow-up was only five months in the dabrafenib group.

The BRIM-3 trial was a large open-label RCT in which an independent review committee was blinded to treatment allocation; it is unclear whether randomisation was carried out appropriately, the treatment groups were generally similar at baseline, an appropriate intention-to-treat analysis was performed and there were no unexpected imbalances in drop-outs between treatment groups.[7] However, median follow-up was less than a year in both groups.

Superseded – see Erratum

The MS also referred to trials CA184-004 and CA184-022, despite these full trials not meeting the inclusion criteria for the review (they included only a small number of chemotherapy-naïve patients). The CA184-004 trial was a small double-blind phase II trial, underpowered to detect a statistically significant difference in overall survival; it is unclear whether randomisation was carried out appropriately, the treatment groups were generally similar at baseline (although more patients in the 10 mg/kg treatment group had stage M0 or M1c disease), median follow-up was less than 9 months in both groups.[13] The CA184-022 trial was a reasonably large double-blind randomised dose-ranging phase II trial; randomisation appears to have been carried out appropriately, the treatment groups were generally similar at baseline (although more patients in the 10 mg/kg treatment group had elevated levels of lactate dehydrogenase and more patients in the 0.3 mg/kg treatment group had stage M1c disease), an appropriate intention-to-treat analysis was performed and there were no unexpected imbalances in drop-outs between treatment groups.[12]

4.2.2.2 Non-RCT evidence

Results of the quality assessment for the non-RCT evidence were presented in Appendix 7 of the MS. Whilst the quality of the three studies was generally adequate, there is a high risk of bias associated with these study designs, relative to an RCT. The manufacturer acknowledged the potential biases introduced through the use of retrospective observational data and pooled analyses. Due to the nature of the evidence and the double-counting between studies included in the pooled dataset and the RCT evidence presented, the ERG does not consider that these studies provide additional relevant reliable data.

In the manufacturer's response to the ERG's points for clarification document they also presented the results of an additional pooled analysis.[14] However, no methods for the pooled analysis were presented; therefore, it is not possible to determine the reliability of the results of this pooled analysis.

4.2.3 Summary of the results of the included trials

4.2.3.1 RCT evidence

Overall survival results for patients enrolled in the four RCTs are presented in Table 4.5 (Table 16 of the MS). The individual study results are then presented separately.

Table 4.5 Overall survival of patients enrolled in CA184-024, MDX010-08, BREAK-3 and BRIM-3

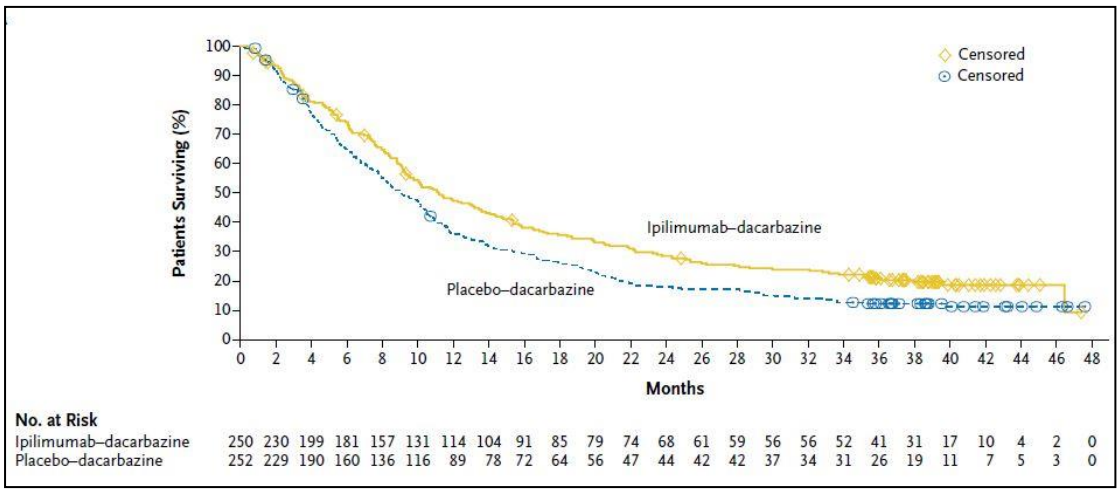
Trial no. (acronym)	Treatment arm	Median OS, months (95% CI)	Hazard Ratio (95% CI)
CA184-024[5]	Ipilimumab 10mg/kg + DTIC DTIC	11.2 (9.4, 13.6) 9.1 (7.8, 10.5)	0.72 (0.59, 0.87)
MDX010-08[6]	Ipilimumab 3mg/kg + DTIC Ipilimumab 3mg/kg	14.3 (10.2, 18.8) 11.4 (6.1, 15.6)	0.75 (0.45, 1.24)
BREAK-3[8]	Dabrafenib DTIC	Not reported	0.61 (0.25, 1.48)
BRIM-3[7]	Vemurafenib DTIC	13.2 (12.0, 15.0) 9.6 (7.9, 11.8)	0.62 (0.49, 0.77)

Superseded – see Erratum

Ipilimumab 10 mg/kg plus DTIC versus DTIC plus placebo (CA184-024)

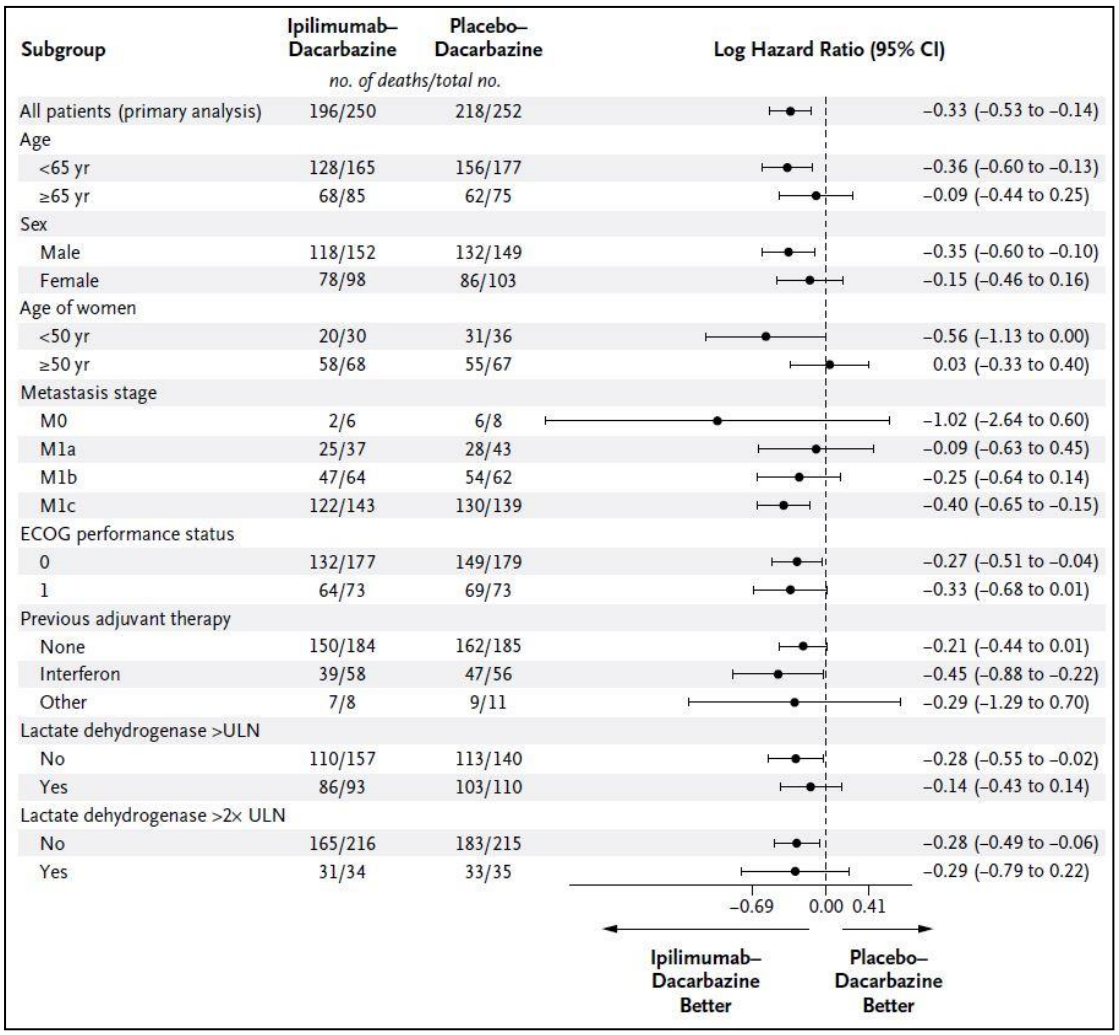
The CA184-024 trial demonstrated that ipilimumab 10 mg/kg plus DTIC (including a maintenance phase of ipilimumab therapy) significantly increased overall survival, compared with DTIC plus placebo, in patients with previously untreated, advanced melanoma.[5] Median overall survival was increased by 2.1 months (11.2 months versus 9.1 months; $p<0.001$), as shown in Table 4.5. Overall survival rates were higher with ipilimumab plus DTIC than DTIC plus placebo at one year (47.6% versus 36.4%), two years (28.9% versus 17.8%), three years (21.3% versus 12.1%), four years (19.1% versus 9.7%) and five years (18.2% versus 8.8%).[28] The Kaplan-Meier curve for overall survival is presented as Figure 4.1 (Figure 10 of the MS).

Figure 4.1 Kaplan-Meier curve for overall survival of patients enrolled in CA184-024



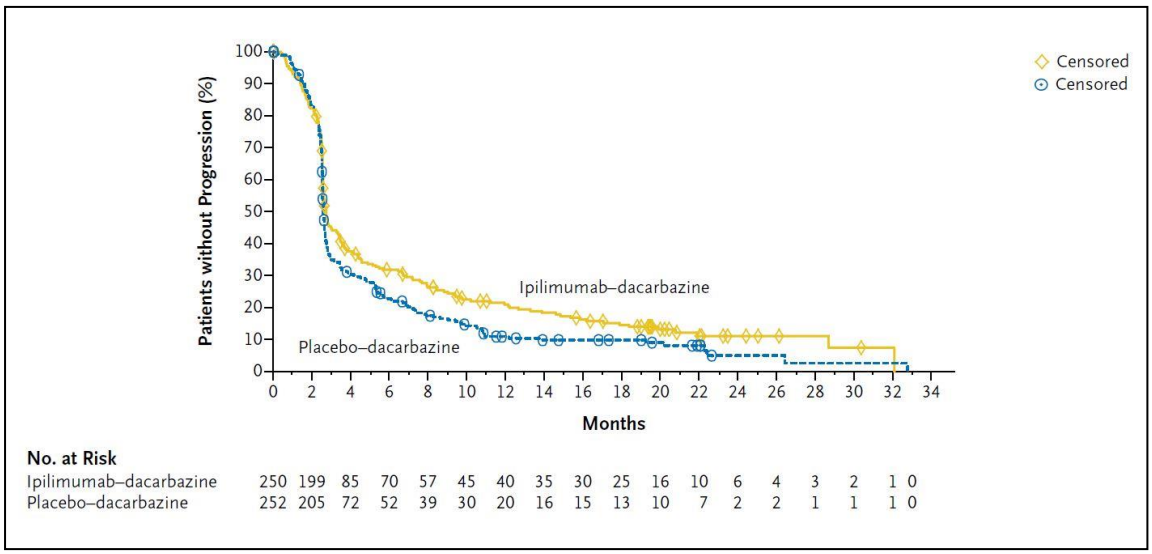
Pre-planned subgroup analyses were conducted in the CA184-024 trial based on the following participant characteristics: M-stage, baseline lactate dehydrogenase level, age, female age, ECOG status, prior adjuvant therapy, race and gender. The results were generally consistent with those for the main analysis, as demonstrated in Figure 4.2 (Figure 11 of the MS). However, for women aged 50 years or over results were less favourable for ipilimumab. The number of patients included in this subgroup analysis was small; therefore, no definitive conclusions can be drawn from these data. The ERG requested the Kaplan-Meier curve for overall survival for the subgroup of patients with stage M1c disease; this was consistent with the main overall survival Kaplan-Meier curve.

Figure 4.2 Overall survival according to subgroup analysis of patients enrolled in CA184-024



There was no statistically significant difference in median progression free survival between ipilimumab plus DTIC and DTIC plus placebo (2.8 months versus 2.6 months), although there was a significant difference in the number of disease progression events (203 versus 223; HR 0.76, 95% CI 0.63 to 0.93; p=0.0064). The Kaplan-Meier curve for progression-free survival is presented as Figure 4.3 (Figure 14 of the MS).

Figure 4.3 Kaplan-Meier curve for progression-free survival of patients enrolled in CA184-024



The response rate was significantly improved with ipilimumab plus DTIC compared with DTIC plus placebo (15.2% versus 10.3%; P=0.03) and the duration of response was significantly longer (median 19.3 months versus 8.1 months; P=0.03). Although there was no significant difference in disease control rate (which included response and stable disease rates) or time to response.

Health related quality of life was measured using the EORTC QLQ C-30 questionnaire. There were no significant differences in EORTC QLQ-C30 functioning scales or symptom scales between ipilimumab plus DTIC and DTIC plus placebo treatment groups. The MS stated that published criteria suggests a mean change in health related quality of life scores of 5 to 10 points indicates "a little" change either for improvement or worsening; a mean change of 10 to 20 points is considered "a moderate" change and 20 points or more is considered "very much" change. At week 12 there were no clinically meaningful changes observed for emotional functioning, pain, insomnia, constipation or diarrhoea. "A little" deterioration was seen for physical functioning and cognitive functioning, and there was "a little" increase in symptoms of nausea/vomiting, dyspnoea, and appetite loss. "Moderate" declines were observed for global health status, role functioning and social functioning, and a "moderate" increase in fatigue was also seen.

On-study adverse events (adverse events reported between the first dose and 70 days after the last dose of the study drug) occurred in more patients who were taking ipilimumab plus DTIC, compared with those taking DTIC plus placebo; particularly gastrointestinal adverse events (36.4% versus 24.7%), pruritis (29.6% versus 8.8%), rash (24.7% versus 6.8%), pyrexia (36.8% versus 9.2%), chills (11.3% versus 4.0%), weight loss (10.9% versus 5.2%), increase in alanine aminotransferase (33.2% versus 5.6%; grade 3 increase in alanine aminotransferase 16.2% versus 0.8%; grade 4 increase in

alanine aminotransferase 5.7% versus 0%) and increase in aspartate aminotransferase (29.1% versus 5.6%; grade 3 increase in aspartate aminotransferase 14.6% versus 1.2%).

The most common treatment related adverse events associated with ipilimumab were immune-related adverse events, which occurred twice as often in patients taking ipilimumab plus DTIC compared with DTIC plus placebo; 77.7% versus 38.2% (grade 3 immune-related adverse events 31.6% versus 3.2%; grade 4 immune-related adverse events 10.1% versus 2.8%); immune-related diarrhoea (32.8% versus 15.9%), immune-related colitis (4.5% versus 0%).

The proportion of patients with grade 3-4 adverse events was twice as high in the ipilimumab plus DTIC treatment group as the DTIC plus placebo treatment group (56.3% versus 27.5%).

A total of 46.2% patients in the ipilimumab plus DTIC group suffered an adverse event leading to study drug discontinuation, compared with 18.3% in the DTIC plus placebo group. Discontinuations due to study-drug toxicity resulted in only 92 patients (37.2%) randomised to ipilimumab plus DTIC receiving all four doses of ipilimumab therapy. Seventy-eight patients (31.6%) received three doses, 45 patients (18.2%) received two doses and 32 patients (13.0%) only received one dose. There were no dose adjustments for any patients in the induction phase (response to points for clarification).[14]

Of the 68 patients in the ipilimumab plus DTIC treatment group who survived more than 2 years, 39 (57.4%) experienced a new onset adverse event more than 70 days after the last dose of ipilimumab was administered; 25 patients experienced a low grade adverse event, whilst 14 experienced a grade 3 or 4 new onset adverse event. In comparison, 14 of 44 (31.8%) patients in the DTIC plus placebo treatment group who survived more than 2 years experienced a new onset adverse event more than 70 days after the last administration; 4 of which experienced a grade 3 or 4 new onset adverse event. 10 (14.7%) ipilimumab plus DTIC patients experienced a new onset immune-related adverse event more than 70 days after the last dose of ipilimumab was administered; 8 patients experienced a low grade immune-related adverse event, whilst two experienced a grade 3 or 4 new onset immune-related adverse event.[14]

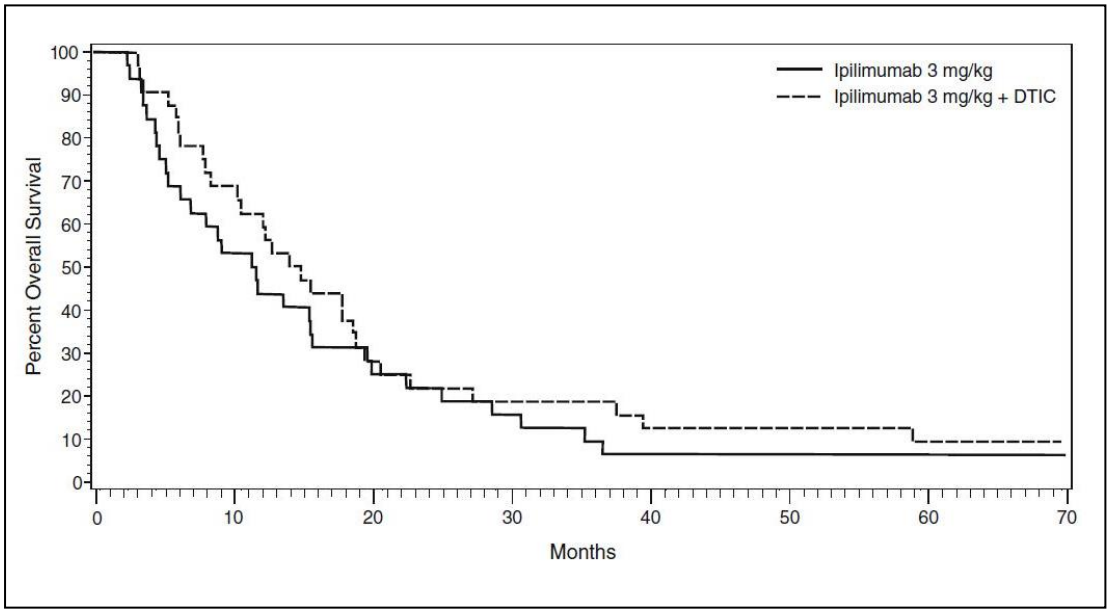
Of the patients who survived less than 2 years, the proportion of patients who experienced a new onset adverse event more than 70 days after the last dose of drug administration was similar between the ipilimumab plus DTIC group and the DTIC plus placebo group.

Ipilimumab 3 mg/kg plus DTIC versus ipilimumab alone (MDX010-08)

The MDX010-08 trial demonstrated that there was no statistically significant difference in overall survival between patients who were treated with ipilimumab 3 mg/kg plus DTIC and ipilimumab alone in patients with previously untreated, advanced melanoma, as shown in Table 4.5, although

results appeared to favour ipilimumab plus DTIC (median overall survival 14.3 months versus 11.4 months; one year overall survival rate 62% versus 45%).[6] However, this trial was under powered to detect a statistically significant difference in overall survival; the analysis only included 64 patients. The Kaplan-Meier curve for overall survival is presented as Figure 4.4 (Figure 12 of the MS).

Figure 4.4 Kaplan-Meier curve for overall survival of patients enrolled in MDX010-08



There was no statistically significant difference in median progression-free survival between ipilimumab plus DTIC and ipilimumab alone; HR 0.642 (95% CI 0.383 to 1.075).[14] In addition, there was no statistically significant difference in the primary outcome of response rate between ipilimumab plus DTIC and ipilimumab alone.

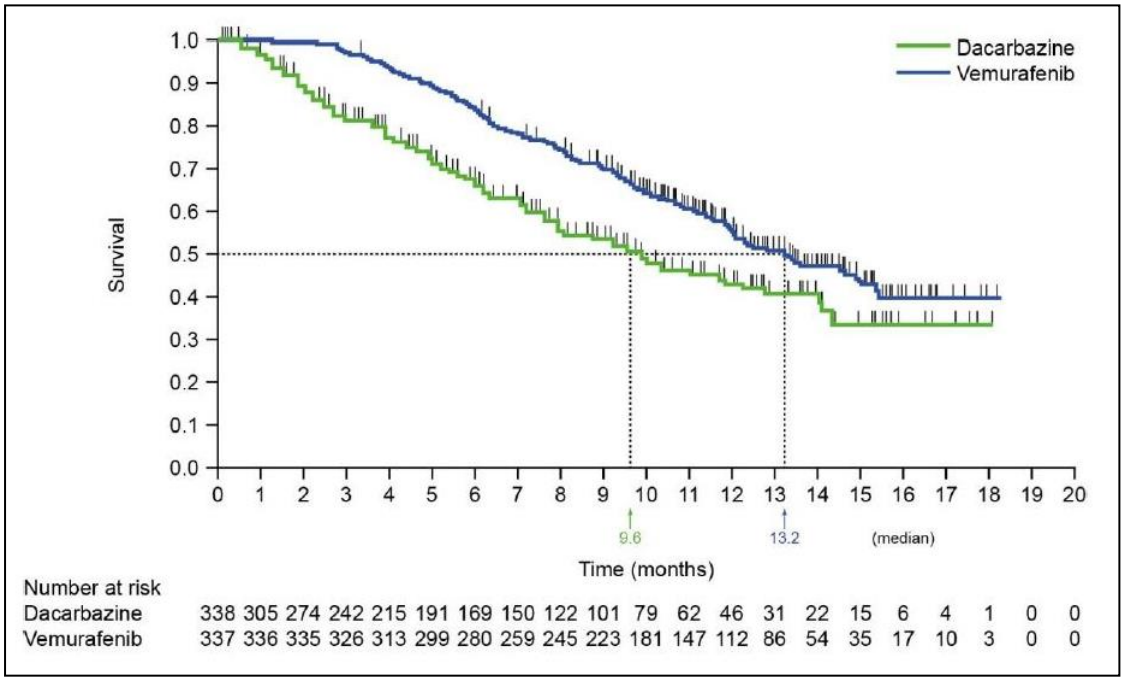
All patients in both treatment groups experienced at least one adverse event and rates of severe adverse events were similar between ipilimumab plus DTIC and ipilimumumab alone groups. However, more patients in the ipilimumab plus DTIC group experienced a serious adverse event (37.1% versus 28.2%), a drug-related adverse event (88.6% versus 74.4%), an immune-related adverse event (65.7% versus 53.8%) or an adverse event leading to drug discontinuation (8.6% versus 2.6%). Adverse events of grade 3 or higher occurred in 22.9% of patients in the ipilimumab plus DTIC group and 12.8% of patients in the ipilimumab alone group.[6]

Vemurafenib versus DTIC in BRAF V600 mutation positive patients (BRIM-3)

The BRIM-3 trial demonstrated that vemurafenib significantly increased overall survival, compared with DTIC, in patients with previously untreated, advanced melanoma that tested positive for the BRAF V600 mutation.[7] Median overall survival was increased by 3.6 months (13.2 months versus 9.6 months; $p<0.001$), as shown in Table 4.5. Overall survival rates were higher with vemurafenib

than DTIC at six months (84% versus 64%). The Kaplan-Meier curve for overall survival is presented as Figure 4.5 (Figure 13 of the MS). Subgroup analysis results were consistent with those for the main analysis, according to tumour stage, baseline lactate dehydrogenase level, age, ECOG status, gender and geographical location.

Figure 4.5 Kaplan-Meier curve for overall survival of patients enrolled in BRIM-3



Progression-free survival was also significantly increased for patients in the vemurafenib treatment group; median progression-free survival 5.3 months versus 1.6 months, hazard ratio for tumour progression 0.26 (95% CI 0.20 to 0.33; P<0.001).

The response rate was significantly improved with vemurafenib compared with DTIC (48.4% versus 5.5%; P=<0.001), time to response was 1.5 months for vemurafenib, compared with 2.7 months for DTIC, although duration of response was not reported.

The most common adverse events in the vemurafenib group were cutaneous events, arthralgia and fatigue. The most common grade 3 adverse events were cutaneous squamous cell carcinoma (12%), rash (8%) and keratoacanthoma (6%). Very few patients experienced a grade 4 adverse event. Adverse events led to dose modification or interruption in 38% of patients. The most common adverse events in the DTIC group were fatigue, nausea, vomiting and neutropenia. Very few adverse events were grade 3 or 4, with the exception of neutropenia, which was grade 3 in 5% of patients and grade 4 in 3% of patients. Adverse events led to dose modification or interruption in 16% of patients.

Dabrafenib versus DTIC in BRAF V600 mutation positive patients (BREAK-3)

Data from the BREAK-3 trial were not mature enough to demonstrate a significant difference in overall survival between dabrafenib and DTIC in patients with advanced melanoma that tested positive for the BRAF V600 mutation, who had not received previous antitumour therapy other than interleukin-2.[8] The median duration of follow-up for patients receiving dabrafenib was only five months. The hazard ratio for death was 0.61 (95% CI: 0.25 to 1.48).

There was a statistically significant increase in progression-free survival for patients in the dabrafenib treatment group; median progression-free survival 5.1 months versus 2.7 months, hazard ratio for tumour progression 0.30 (95% CI 0.18 to 0.51; P<0.0001).

The response rate was 52.9% for dabrafenib and 19.0% for DTIC, disease control rate was 91.4% for dabrafenib and 54.0% for DTIC. The median time to response with dabrafenib was 1.6 months and the median duration of response was 5.6 months.

Fifty-three percent of patients in the dabrafenib group and 44% of patients in the DTIC group experienced an adverse event. The most common adverse events in patients receiving dabrafenib were cutaneous (hyperkeratosis, papillomas, palmar-plantar erythrodysaesthesia), pyrexia, fatigue, headache and arthralgia. Six percent of patients developed a cutaneous squamous cell carcinoma. Very few adverse events were grade 3 or 4. Dose reduction of dabrafenib was needed in 28% patients and 3% patients discontinued treatment because of adverse events. In patients receiving DTIC the most common adverse events were nausea, vomiting, fatigue and neutropenia. Few adverse events were grade 3 or 4, with the exception of neutropenia, which was grade 3 in 5% of patients and grade 4 in 7% of patients. Dose reduction of DTIC was needed in 17% patients and 3% patients discontinued treatment because of adverse events.[8]

Ipilimumab results from additional trials (CA184-004 and CA184-022)

The MS also referred to trials CA184-004 and CA184-022, despite these full trials not meeting the inclusion criteria for the review. The CA184-004 trial found no meaningful differences in clinical activity between ipilimumab 3 mg/kg and 10 mg/kg.[13] In the CA184-022 trial, best overall response rate (11.1% versus 4.2%), median overall survival (11.4 months versus 8.7 months) and progression-free survival at 24 weeks (18.9% versus 12.9%) appeared to be better in the 10 mg/kg treatment group, compared with the 3 mg/kg treatment group.[12] There was a statistically significant increase in best overall response rate with increasing dose of ipilimumab. However, median overall survival was not statistically significantly different between treatment groups (HR 0.875, 95% CI 0.593 to 1.291). Grade 3 or 4 adverse events were more common in the 10 mg/kg treatment group.

4.2.3.2 Non-RCT evidence

Interim results from two ongoing retrospective observational studies

Median overall survival for the CA184-332 and CA184-338 observational studies was 11.5 months and 14.3 months, respectively. Estimated one year survival rates were 49% and 60% respectively.[9, 10]

Pooled analysis of treatment-naïve or chemotherapy-naïve advanced melanoma patients

Median overall survival for the pooled analysis was 13.5 months (95% CI 11.2 to 19.6). The estimated one year survival rate was 54% and the estimated two year survival rate was 31.6%.[11]

Additional pooled analysis presented

In response to the ERG's points for clarification document, the manufacturer also reported the results of a pooled data analysis that was submitted for the STA "ipilimumab in previously treated unresectable malignant melanoma" (TA268), which compared overall survival profiles of ipilimumab 3 mg/kg (MDX010-20 and CA184-022) and 10 mg/kg (CA184-007, CA184-008 and CA184-022) for a mixed population of both previously treated and untreated patients. The results of this pooled analysis suggested that a 10 mg/kg dose is better than a 3 mg/kg dose in terms of overall survival, as displayed in the Kaplan Meier curve presented in Figure 4.6 below.[14]

Figure 4.6 Kaplan-Meier curve for overall survival profiles for ipilimumab 3 mg/kg and 10 mg/kg: pooled dataset

*95% confidence intervals denoted by dashed lines

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The trials included in the indirect comparisons were CA184-024, BREAK-3 and BRIM-3, described in section 4.2, with DTIC being the common comparator treatment in each of the trials.[5, 7, 8]

A mixed treatment comparison (MTC) was undertaken using hazard ratios of death to populate the MTC analysis. In addition, adjusted indirect comparisons of ipilimumab plus DTIC versus vemurafenib and dabrafenib were calculated, using the Bucher method.

The mixed treatment comparison analysis of the complete network of evidence demonstrated no significant difference in survival between ipilimumab plus DTIC and the BRAF inhibitors vemurafenib and dabrafenib (Figure 19 of the MS). The pair wise indirect comparisons using the Bucher equation also showed no significant differences in survival between ipilimumab plus DTIC and the BRAF inhibitors vemurafenib (indirect hazard ratio 1.16, 95% CI 0.86 to 1.56) and dabrafenib (indirect hazard ratio 1.18, 95% CI 0.48 to 2.93).

The MS acknowledged that there were a number of limitations with the indirect comparisons, including the differences in patient characteristics between the trials. In addition, there are differences in the mechanism of action between ipilimumab and BRAF inhibitors, resulting in different Kaplan-Meier curve shapes for overall survival, so the hazard ratios across trials may not be proportional. The study design also differed between the three trials.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The ERG does not consider the indirect comparisons of ipilimumab, vemurafenib and dabrafenib to be appropriate because of differences in patients' baseline characteristics between the trials; a higher proportion of patients in the vemurafenib and dabrafenib trials had elevated serum lactate dehydrogenase levels and M1c disease than patients in the ipilimumab trial. These are prognostic factors associated with poorer outcomes.

4.5 Conclusions of the clinical effectiveness section

The CA184-024 trial demonstrated that ipilimumab 10 mg/kg plus DTIC (including a maintenance phase of ipilimumab therapy) significantly increased overall survival compared with DTIC plus placebo, in patients with previously untreated, advanced melanoma.[5] This was a large good quality trial; therefore, the results are likely to be reliable. However, this trial does not provide direct evidence for the clinical effectiveness of ipilimumab 3 mg/kg monotherapy (without maintenance therapy) compared with DTIC, vemurafenib or dabrafenib for the treatment of previously untreated, advanced melanoma patients.

The MS seeks to demonstrate that a 3 mg/kg dose of ipilimumab is equivalent to a 10 mg/kg dose in terms of overall survival using data from trials that were not included in the systematic review. In the CA184-022 trial of previously treated and untreated patients median overall survival appeared to be better in the 10 mg/kg treatment group, compared with the 3 mg/kg treatment group; although the difference was not statistically significant.[12] A very small trial of previously treated and untreated patients (CA184-004) found no meaningful differences in clinical activity between the two ipilimumab doses.[13] In the manufacturer's response to the ERG's points for clarification document, the manufacturer presented the results of a pooled data analysis in both previously treated and untreated patients, which also suggested that a 10 mg/kg dose is better than a 3 mg/kg dose in terms of overall survival.[14] Therefore, there is currently no conclusive evidence that ipilimumab at a dose of 3 mg/kg is as clinically effective as a dose of 10 mg/kg.

The MS cites the MDX010-08 trial as evidence for the equivalence of ipilimumab monotherapy and ipilimumab plus DTIC.[6] The results of this very small (n=64 patients) trial suggest that ipilimumab plus DTIC is more effective than ipilimumab alone, however, the trial was underpowered to detect a statistically significant difference for overall survival. Therefore, there is no conclusive evidence that ipilimumab monotherapy is as clinically effective as ipilimumab plus DTIC.

Therefore, based on the evidence presented, the ERG considers that the survival benefit may be overestimated in the MS.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the manufacturer and the additional information provided following the ERG points for clarification. The submission was subject to a critical review on the basis of the manufacturer's report and by direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of economic evaluations and a narrative review to highlight key assumptions and possible limitations. Section 6 presents additional work undertaken by the ERG to address some remaining uncertainties.

The manufacturer's economic submission included:

1. A description of the systematic literature review conducted to identify economic evaluations of ipilimumab for the treatment of previously untreated advanced (unresectable or metastatic) malignant melanoma (Manufacturer's Submission (MS), Section 7.1) with details in a separate appendix (MS, Appendix 10).
2. A report on the de novo economic evaluation conducted by the manufacturer. The report described the patient population, model structure, technology and comparators (MS, Section 7.2); clinical parameters, modelling techniques employed and assumptions made to model the clinical outcomes (MS, Section 7.3); the assumptions and sources of evidence used to assess quality of life (MS, Section 7.4); the resource use and unit cost assumptions and sources (MS, Section 7.5); the sensitivity analyses undertaken (MS, Section 7.6); and the cost-effectiveness results for the base-case and sensitivity analysis (MS, Section 7.7).
3. An electronic copy of the manufacturer's economic model developed in Microsoft Excel®.

In response to a number of points for clarification raised by the ERG, the manufacturer further submitted:

4. A descriptive reply to the ERG's points for clarification, as well as appendices with additional data requested by the ERG.[14]
5. An updated Excel-based model, which incorporated additional cut-off points for Kaplan-Meier data from the CA184-024 trial[5] before fitting a parametric survival model to the trial data.

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Searches

The manufacturer undertook a systematic literature review to identify cost-effectiveness studies relevant to this appraisal of ipilimumab for the treatment of previously untreated advanced (unresectable or metastatic) malignant melanoma. The search strategies were described in the main body of the submission, and full details were provided in the Appendices.

The electronic databases MEDLINE, MEDLINE In Process, EMBASE, EconLIT, the Cochrane Library (including NHS EED, the Cochrane Database of Systematic Reviews, the Health Technology Assessment Database and the Database of Abstracts of Reviews of Effects (DARE)) and CINAHL were searched. In addition to the formal electronic searches, reference lists of included cost-effectiveness and quality-of-life studies were hand searched for additional relevant studies. Searches for each database were reported in Appendix 10, Section 10.10 of the MS.

The searches were performed on the 9th May 2013 and covered the period 1946-May 2013 for MEDLINE and MEDLINE In-Process, 1974- May 2013 for EMBASE, 1996-May 2013 for Cochrane Database of Systematic Reviews, 1995-May 2013 for HTA database, DARE and NHS EED, 1981-May 2013 for CINAHL and 1961-April 2013 for EconLit. Several of the databases had a date limit of 1970 applied to the results of the searches: MEDLINE and MEDLINE In-process, Cochrane Database of Systematic Reviews, HTA database, DARE and NHS EED. No language restrictions were applied.

Generally, the search strategies were well reported in the MS. The exact strategies used along with the databases searched, the database service provider, dates of searches and date span of the searches were all clearly reported. All of the NICE specified databases were searched.

As with the clinical evidence searches, the textword and subject headings used in the search strategies for ipilimumab and the comparator drugs were appropriate. Various synonyms and spelling variations for melanoma or skin cancer have been included in the strategy. However neoplas$ and tumor$ have not been included. Boolean operators, truncation and field searches have been used appropriately. A precise economics filter developed by SIGN was used to limit retrieval to economic studies.

5.1.2 Inclusion/exclusion criteria used for study selection

To be considered relevant to the analysis, the identified studies had to be full economic evaluations, i.e. cost-consequence, cost-minimisation, cost-effectiveness, cost-utility and cost-benefit evaluations that compared ipilimumab to one or more of its comparators. The comparators included in the search were DTIC, dabrafenib and vemurafenib. Letters, editorials and reviews of economic evaluations were excluded, although reference lists of the latter were hand-searched. The ERG considers the

inclusion/exclusion criterion to be reasonable and would have been expected to identify any relevant studies.

5.1.3 Studies included and excluded in the cost effectiveness review

204 studies were initially identified. 197 of the 204 studies were excluded during primary filtering, either for being the wrong study type (n=184), wrong line of treatment (n=6), wrong intervention (n=4) or a duplicate/review (n=3). Of the seven studies remaining for secondary filtering, six were the wrong study type and one was using the wrong intervention. The MS did not explicitly state that the review was aimed only at studies investigating ipilimumab as a first-line treatment. However, the ERG assumed this to be the case as one of the exclusion criteria was 'wrong line of treatment' and the cost-effectiveness analysis conducted for the previous submission of ipilimumab (TA268) was not included in the search results.

5.1.4 Conclusions of the systematic review

The manufacturer's search did not identify any relevant economic assessments of ipilimumab as a first line treatment. Therefore, the ERG considered the cost-effectiveness analysis reported in the current submission to be the most relevant source of evidence to inform the decision problem.

5.2 ERG's summary and critique of manufacturer's submitted economic evaluation

An overall summary of the manufacturer's approach and signposts to the relevant sections in the MS are reported in Table 5.1 below:

Table 5.1 Summary of the Manufacturer's economic evaluation (and signposts to manufacturer's submission)

	Approach	Source / Justification	Location in MS
Model	A semi-Markov model was employed for the cost-effectiveness analysis.	The model tried to reflect the pattern of care routinely provided by the NHS in a UK clinical context.	Section 7.2.2; p114-115
States and events	The model included 5 health states: first-line, second-line and third-line treatment, palliative care and death. Disease progression was used as a proxy for movement between the lines of treatment.	The model health states were designed to represent the lines of treatment and to account for the costs and outcomes associated with each line of treatment.	Section 7.2.2; p114-115 Section 7.2.3; p116
Comparators	Ipilimumab was compared with: 1. DTIC 2. vemurafenib	The main comparators were therapeutics currently approved for first-line use in advanced melanoma in the UK, as identified by the NICE scope.[4] Dabrafenib was used in the indirect comparison analysis but it was excluded from the CE model, as it is not currently approved for first-line use, nor was it listed in the NICE scope.	Section 7.1.1; p110-111; Section 7.2.1; p113
Natural History	Based on semi-Markov model. The health states in this model were defined as treatment lines (i.e. first line, second line, third line) although disease progression was used as a proxy for movement between the lines of treatment.	Disease progression and patient movements from one line of treatment to the next were based on PFS as reported in the clinical trials. This measure would be expected to be used by clinicians to determine the appropriate timing for a change of therapy.	Section 7.2.3; p116 Section 7.2.5; p117
Treatment effectiveness	OS for first-line ipilimumab and first-line DTIC was modelled using a 3 part curve fit. First-line vemurafenib OS was modelled as is reported in the previous NICE STA (TA269) of vemurafenib. OS in second-line treatments was derived by adjusting the first-line survival curves such that they account for poorer outcomes on second-line treatment. PFS was used as a proxy for change of therapy.	OS for first-line ipilimumab: the 3-part curve consisted of Kaplan–Meier data up to 2 years (CA184-024 trial),[5] a fitted parametric curve up to 5 years and long-term registry data from the American Joint Committee on Cancer (AJCC) from 5 years onwards.[29] First-line vemurafenib OS: trial Kaplan–Meier data up to 14 months followed by three different monthly risks of death between months 14 and 46.[20] After this point, the curve switched to fit to registry data from the AJCC.[29] For modelling PFS, a 2 part curve fit was used for all	Section 7.3.2; p121-139

	Approach	Source / Justification	Location in MS
		technologies. OS of patients on second-line treatments: the hazard ratio (HR) derived from the expected life years achieved by patients from the second-line NICE appraisal for ipilimumab (TA268) was used.[1]	
Adverse events	The inclusion criteria for adverse events in the model were any grade 3+ event, or grade 2+ for diarrhoea, with an incidence greater than or equal to 3%. In addition all endocrine disorders were included.	Adverse events for patients treated with ipilimumab were taken from the CA184-024 clinical trial.[5] Event incidences for patients treated with vemurafenib were taken from Chapman et al. (BRIM-3 trial).[7] Costs for adverse events were applied at the start of the model for first-line treatments, and in the first cycle of treatment for second and third lines. Utility decrements from AEs were already incorporated in the utility equations.	Section 7.3.2; p138-139 Section 7.4.8; p155-156
Health-related quality of life	Health-related quality of life (HRQL) outcomes were quantified using sub-health states in the model, based on the time to death (instead using of pre- and post-progression health outcomes)	Time to death showed the greatest correlation with utility in tests of the impact of time dependent variables upon utility using data from CA184-024[5] and MDX010-20. HRQL data were collected in the CA184-024 trial using the EORTC QLQ-C30.[5,30] Utilities were derived using the valuation algorithm produced by Rowen et al.[31]	Section 7.4.3; p146-151 Section 7.4.9; p156-157
Resource utilisation and costs	Cost categories were as follows: drug acquisition costs (including PAS for ipilimumab and vemurafenib); drug administration; resource use costs; treatment of adverse effects.	The NHS Reference costs 2011/2012 for delivery of chemotherapy were used to cost administration in the model.[32] Drug acquisition costs were taken from eMIT (October 2013)[33] and BNF (September 2013).[34] Resource use unit costs were derived from NHS Reference costs 2011/2012[32] and PSSRU	Section 7.5; p160-177

	Approach	Source / Justification	Location in MS
		2012.[35] The costs of adverse events were sourced from the NHS Reference costs[32] and from the Oxford Outcomes report.[36]	
Discount rates	An annual rate of 3.5% was used for both costs and health effects	In accordance with the NICE Guide to the Methods of Technology Appraisal.[37]	Section 7.2.6; p118
Population and Subgroups	The main population considered was adults with advanced (unresectable or metastatic) previously untreated melanoma. In the model, two sub-populations were considered: BRAF V600 mutation-positive patients and BRAF V600 mutation-negative patients.	The main population was chosen as relevant to the decision problem. Subgroups were chosen to address the licensed indications of treatments (i.e. to identify the suitability for treatment with BRAF inhibitors)	Section 7.1.1; p110-111; Section 7.2.1; p113
Sensitivity analysis	Deterministic sensitivity analysis was performed on a series of model parameters, only for the BRAF V600 mutation-positive population. Probabilistic sensitivity analysis and scenario analyses were also performed.	In accordance with the NICE reference case.	Section 7.7.7; p193-203

DTIC, dacarbazine; AJCC, American Joint Committee on Cancer; OS, overall survival; PFS, progression free survival; AE, adverse event; BNF, British National Formulary; eMit, Electronic Market Information Tool; BSC, best supportive care; NHS, National Health Service; CE, cost-effectiveness

5.2.1 The manufacturer's economic evaluation compared with the NICE reference case checklist

Table 5.2 summarises the economic submission and the ERG's assessment of whether the de novo evaluation meets NICE's reference case and other methodological recommendations.

Table 5.2 NICE reference case list

Attribute	Reference Case	Included in MS	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Comparator(s)	Alternative therapies in the NHS, including those currently regarded as current best practice	Yes	The analysis included all relevant comparators, as described in the final scope issued by NICE. However, in the treatment sequencing approach that was followed, not all possible treatment pathways were modelled. Dabrafenib was not in the scope and does not meet the reference case for comparators, defined as 'therapies routinely used in the NHS, including technologies regarded as current best practice'.
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective - costs	NHS and PSS	Yes	NHS and PSS costs were taken into account.
Perspective - benefits	All health effects on individuals	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model followed a life-time horizon (40 years). Less than 0.001% of patients were expected to be alive beyond this period.
Synthesis of evidence on outcomes	Systematic review	Yes	A systematic review on clinical effectiveness was conducted. The trials that met the systematic review criteria were synthesised via a Mixed Treatment Comparison analysis. The outcomes of this analysis, however, were not used in the cost-effectiveness model.
Outcome measure	QALYs	Yes	HRQL outcomes were quantified using sub-health states in the model, based on the time to death.
Health states for QALY measurement	Described using a standardised and validated instrument	Yes	HRQL data were collected in the CA184-024 trial using the EORTC QLQ-C30 questionnaire.[5,30] Utilities have been derived from the EORTC QLQ-C30 using the valuation algorithm produced by Rowen et al.[31]
Benefit valuation	Time Trade Off or Standard Gamble	Yes	Time Trade Off
Source of preference data	Representative sample of the public	Yes	The utilities used were broadly consistent with the NICE reference case; the valuation algorithm uses an instrument valued by members of the general population using time trade off and the utilities are consistent with the utilities from the second-line NICE appraisal for ipilimumab (TA268).[1]

Discount rate	3.5% on costs and health benefits	Yes	Costs and benefits have been discounted at 3.5% per annum.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was conducted as well as deterministic and structural sensitivity analyses. Mean increment results for the probabilistic sensitivity analysis were presented as well as graphical results using scatter plots, cost-effectiveness acceptability curves and cost-effectiveness acceptability curves.
NHS, National Health Service; PSS, personal social services; QALY, quality-adjusted life years; HRQL, health-related quality of life			

5.2.2 Population, intervention and comparators

The MS evaluated the cost-effectiveness of ipilimumab for the treatment of adults with advanced (unresectable or metastatic) malignant melanoma who have not received prior therapy. This is an extension of the second-line indication of ipilimumab for adults with previously-treated advanced malignant melanoma. The intervention considered in the MS is the licensed dose of ipilimumab, i.e. 3mg/kg every 3 weeks for a total of 4 doses. However, the assessment of cost-effectiveness is based on comparative effectiveness evidence on the efficacy of ipilimumab 10mg/kg in addition to DTIC therapy. The lack of comparative studies investigating ipilimumab as a first-line treatment in the 3mg/kg dosing regimen imposes a number of assumptions on the cost-effectiveness analysis. This is discussed further in Sections 5.2.5.3, 5.2.5.4 and 5.2.5.6 and the implications for the cost-effectiveness results are explored in Section 6. The comparators included in the assessment of cost-effectiveness were DTIC and vemurafenib in line with the final scope of NICE.[4] The dosing regimen applied for vemurafenib and DTIC matches their respective SPCs and the recommended dosing in the UK.[38, 39]

In clinical practice, the majority of patients undergo a molecular analysis of their tumour to determine the mutational status of the BRAF V600 gene and consequently the potential for treatment with BRAF inhibitors (e.g. vemurafenib). Therefore, two separate populations were considered in the MS:

- BRAF V600 mutation-positive patients, who are eligible for first-line treatment with ipilimumab, DTIC, or vemurafenib; and
- BRAF V600 mutation-negative patients, who are eligible for first-line treatment with ipilimumab or DTIC.

To establish the cost-effectiveness in these two separate populations, ipilimumab first-line therapy was compared to DTIC or vemurafenib first-line therapy using a pair-wise comparison approach. Furthermore, the cost-effectiveness of first-line therapy is assessed by using a treatment sequencing approach which incorporates second-line active therapy and third-line best supportive care (BSC). This is discussed in detail in Sections 5.2.4 and 5.2.5.6. While the ERG acknowledges that a treatment sequencing approach may provide a more appropriate characterisation of the relevant decision problem faced by the NHS, it is important to recognise that the existing evidence for ipilimumab does not relate to a comparison of sequential use of treatments for previously untreated advanced melanoma.

5.2.3 Perspective, time horizon and discounting

The perspective of the manufacturer's analysis was the NHS and Personal Social Services. An annual discount rate of 3.5% on both costs and health effects was applied, in line with NICE guidance. The time horizon of the model was 40 years (2,087 weekly cycles), which was stated to represent a lifetime horizon for the patient population defined. The ERG considered this an appropriate time horizon as the model predicts that a proportion of less than 0.001% of patients is expected to remain alive beyond 40 years.

5.2.4 Model structure

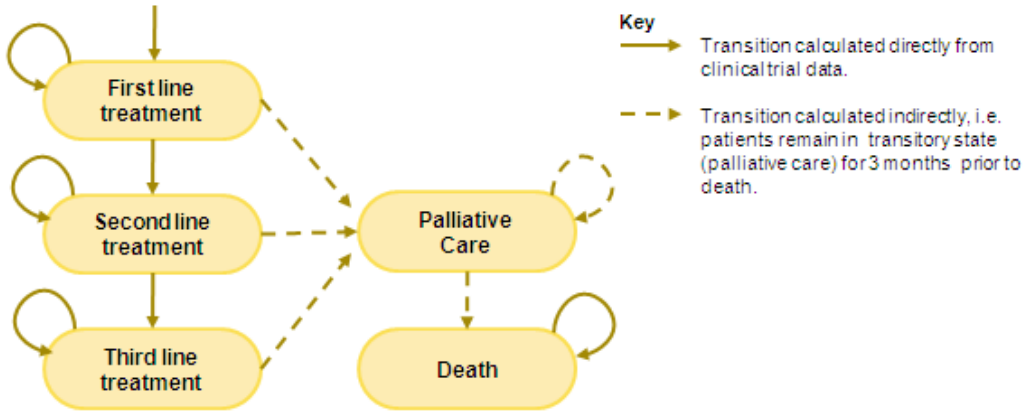
In the absence of any previously published cost-effectiveness analyses of ipilimumab as a first-line therapy, the manufacturer undertook a de novo economic evaluation based on a semi-Markov model. The model projects expected clinical and economic outcomes for patients who were assumed to receive either ipilimumab or the comparator treatment (DTIC or vemurafenib). The model is a cost-utility model with outputs presented for:

- Costs – broken down by type
- Life years gained (LYG) – broken down by health state
- Quality adjusted life years (QALYs) – broken down by health state

In contrast with the previous submission of ipilimumab (TA268),[1] which employed a typical three health-state model for cancer ('non-progressive disease', 'progressive disease' and 'death'), the model developed for this analysis used a 'treatment sequencing' approach. Health states were defined based on the different lines of treatment that patients may follow. Five health states were modelled: first-line treatment, second-line treatment, third-line treatment, palliative care and death. In each weekly cycle, patients could either have stable disease and remain in the same treatment line, progress in disease and consequently move to the next treatment line, or die. In the 12 weeks prior to death, it was assumed that patients would transition to the 'palliative care' state, which takes account of the additional costs

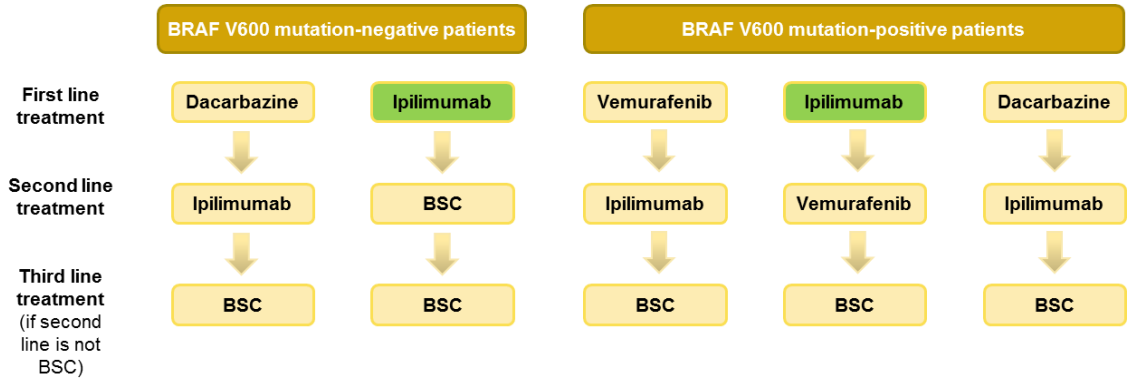
expected to be incurred in providing end of life care. This time period of 12 weeks was shorter compared with the 4 months of palliative care that was used in TA268 for previously treated patients. A schematic representation of the manufacturer's model is shown in Figure 5.1.

Figure 5.1 Economic model structure (simplified)



The transitions to second- and third-line treatment were modelled based on progression-free survival data, while overall survival data was used to model transitions to the 'death' state. The treatment pathways that were modelled for the two sub-populations- BRAF V600 mutation positive and BRAF V600 mutation negative patients- are shown in Figure 5.2.

Figure 5.2 Modelled treatment patterns. BSC (best supportive care): active treatment used off-license; In the final 3 months of life patients are assumed to receive palliative care



The approach used by the manufacturer raises a number of important issues. The first of these relates to the use of a treatment sequencing approach to structure the economic model. This differs principally from the model used in the previous submission of ipilimumab in TA268, which adopted a three- state model for pre-progression, post-progression and death.[1] In the ERG's points for clarification to the manufacturer, the ERG requested further clarification on the rationale for adopting an alternative approach to the assessment of cost-effectiveness of ipilimumab first-line. In response, the manufacturer stated that the model structure was consistent with the previous three-state model of

second-line ipilimumab and that the only difference was that progressive disease, i.e. post progression survival, was split into two health states, second and third line treatment.[14] The manufacturer's rationale for this split was that the current decision problem is for first-line treatment (not second-line) of melanoma, where the model required the ability to look at more than one treatment in sequence since there is now more than one active treatment within this area (i.e. ipilimumab and vemurafenib) and current NICE recommendations allow these treatments to be used in sequence.

Although the ERG recognises that the approval of multiple treatments for advanced melanoma may lead to their sequential use in clinical practice, it is important to note that the existing evidence for ipilimumab does not relate to a comparison of sequential use of treatments for previously untreated advanced melanoma. There are no completed clinical trials comparing the sequential use of treatments for previously untreated advanced melanoma. For example, there is no currently available clinical evidence about the relative effectiveness of ipilimumab first-line followed by vemurafenib second line compared with vemurafenib first-line followed by ipilimumab second line. The manufacturer's attempt to model the sequencing of treatments has led to a major oversimplification of a complex treatment sequencing decision problem. By adopting the approach taken, the manufacturer has been forced to make arbitrary assumptions about overall and progression-free survival on second- and third-line treatments. These assumptions, which are discussed in detail in Section 5.2.5, significantly undermine the validity of the model structure. Furthermore, it is important to note that the clinical evidence from the five-year overall survival curves for ipilimumab and DTIC in the CA184-024 trial already include the impact of progression to subsequent lines of therapy.

The second concern is about the manufacturer's choice of modelled treatment permutations. No justification for the choice of modelled pathways in Figure 5.2 was presented in the MS. For example, DTIC first-line followed by vemurafenib second line was not considered as an option in the model but it was presented as an option in the current clinical care pathway in the MS (Figure 2, p 25). Although there are no concrete clinical guidelines to determine the exact sequence among the currently available therapies (i.e. DTIC, ipilimumab, vemurafenib and BSC), there are certain progressive trends with regard to the treatment of melanoma (e.g. vemurafenib being preferred in first line for patients with BRAF V600 mutation) and the treatment patterns are still largely subject to individual clinicians' discretion. As a result, there are a number of additional treatment permutations that could potentially be applied in clinical practice, which have not been captured in the manufacturer's analysis. This partial and incomplete approach to modelling the treatment sequences, along with the lack of clinical evidence and inconsistent assumptions discussed in Section 5.2.5 below, further undermines the validity of the approach adopted by the manufacturer.

The ERG considers a conventional three-state model structure for progression-free survival, post-progression and death used in most cancers to be more appropriate as it avoids the use of arbitrary assumptions about second- and third-line treatment. The implications of the manufacturer's approach on the cost-effectiveness results are presented and discussed in Section 6. The assumptions made with regard to the treatment sequencing and the ERG's concerns around these are discussed in detail in the following sections.

5.2.5 Treatment effectiveness and extrapolation

The transitions between lines of treatment and the proportion of patients who die in each cycle were informed by extrapolated clinical trial data. Parametric survival curves were fitted to empirical data on overall survival (OS) and progression-free survival (PFS) to enable the observed data to be extrapolated beyond the follow-up period of the trial in order to estimate mean survival times required for the cost-effectiveness analysis. For ipilimumab and DTIC the main source of data used to inform OS and PFS was the respective treatment arms of the CA184-024 trial, which investigated the efficacy of ipilimumab 10mg/kg in addition to DTIC therapy (used to inform the efficacy of ipilimumab) compared with DTIC monotherapy (used to inform the efficacy of DTIC). For vemurafenib, separate, independent OS and PFS data were used to model the comparative efficacy of ipilimumab and vemurafenib, which was informed by the BRIM-3 trial which investigated the efficacy of vemurafenib compared with DTIC in patients testing positive for the BRAF V600 mutation. Clinical disease progression using PFS data was used as a proxy for determining change in therapy, i.e. the movement to the next line of treatment. For second-line treatments, the OS was based on the first-line survival curves but adjusted downwards to account for poorer outcomes on second- line therapy using a constant proportional hazard derived from the expected life years of second-line ipilumumab from TA268. The duration of response to second-line treatments was based on the number of pre-progression life years for second-line ipilumumab from TA268.[1] Third line treatment was assumed to be best supportive care (BSC), which consisted of a proportion of patients on 'no treatment' and a proportion on commonly prescribed chemotherapy drugs, including DTIC. The OS for patients who survived to receive third-line BSC was assumed to be the same as those on first-line treatment who had not progressed to next line of therapy.

Superseded – see Erratum

The ERG has identified several specific issues which relate to the subsequent use of these data in the economic model. The key issues identified by the ERG include:

- The appropriateness of assuming that the absence of evidence for ipilumumab 3mg/kg in previously untreated advanced melanoma implies equal efficacy to ipilimumab 10mg/kg;
- The appropriateness of assuming that concomitant DTIC therapy with ipilimumab 10mg/kg in the CA184-024 trial implies equal efficacy to ipilimumab 10mg/kg monotherapy;

- The use of separate, independent arms from trials to inform the relative efficacy of ipilimumab and vemurafenib (hence breaking randomisation); and
- The appropriateness of the assumptions used to model second- and third-line treatment.

Each of the areas is considered in more detail below, outlining the key assumptions and the potential uncertainties surrounding them.

5.2.5.1 OS on first-line therapy

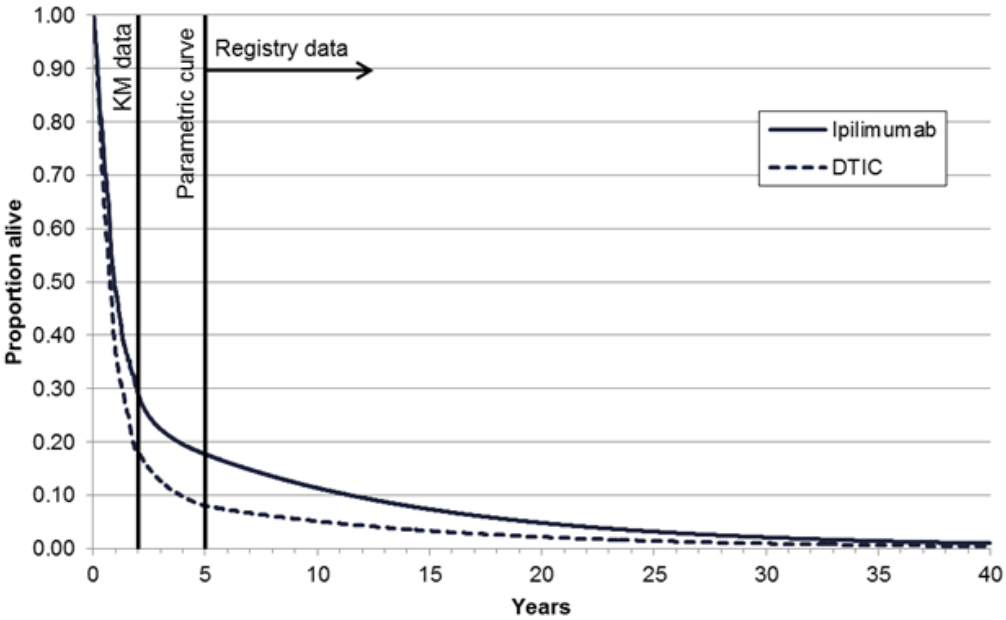
Ipilimumab and DTIC

The CA184-024 trial, which had up to 5 years follow-up, was used to inform OS for first-line ipilimumab and first-line DTIC.[5] A single parametric curve fit to the survival data was not sufficient to model the change in hazards over the duration of the trial period. Therefore, the manufacturer opted for a 3-part curve fit to account for the survival profile observed by patients in the trial. The manufacturer used the NICE Decision Support Unit guidelines for model selection in order to determine the most appropriate curve fits for use in the model.[40] Nelson-Aalen plots were inspected in order to determine the point at which the hazard changed for patients receiving ipilimumab. A 24-month cut-off point was used within the modelling. Based on '24 months' being the point at which the hazard changes, the three-part curve fit consisted of Kaplan–Meier data up to 2 years, a fitted parametric curve up to 5 years, and a curve fitted to long-term registry data from the American Joint Committee on Cancer (AJCC) from 5 years onwards.[29] The manufacturer considered several different survival models for the curve fit: stratified log-normal, log-normal, stratified log-logistic, log-logistic, exponential, stratified Weibull, Weibull, stratified extreme value and extreme value. Of these, a stratified lognormal survival function was fitted to the ipilimumab and DTIC Kaplan-Meier data between years 2 and 5, and a Weibull distribution was fitted to registry data for patients alive at 5 years, based on the best fitting curve as determined by the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Figure 5.3 shows the OS used within the model for first line ipilimumab and DTIC.

The approach used to extrapolate OS for ipilimumab and DTIC is similar to that presented in the manufacturer's revised model of ipilimumab second-line (TA268).[1] The ERG considers this approach to be appropriate but it is important to note that the population under assessment is highly heterogeneous and a 'purely' statistical approach to extrapolation of trial data may not be sufficient to represent unobserved heterogeneity in the patient population. Furthermore, in cases where there is little censoring, the emphasis on statistical goodness of fit (as assessed by the AIC/BIC criteria) may be reasonable for the purposes of extrapolation but, conversely, if censoring is more extensive it may be appropriate to place more weight on the clinical plausibility of the extrapolated curves than on the

statistical goodness of fit. Although the ERG believes that alternative survival models with different cut-off points may have been more appropriate for the OS extrapolation, the cost-effectiveness results for alternative cut-off points for 1.5 and 2.5 years does not significantly impact on the ICER.[14]

Figure 5.3 First-line ipilimumab and DTIC OS 3 part curve fits from the CA184-024 trial



Vemurafenib

The BRIM-3 trial, which examined the relative efficacy of vemurafenib compared with DTIC, was used to inform OS for first-line vemurafenib.[7] The comparative efficacy of ipilimumab and vemurafenib was therefore based on separate, independent treatment arms of different clinical trials (i.e. randomisation was broken). No adjustment was made within the model to take account of differences in the patient populations between BRIM-3 and CA184-024. The manufacturer's justification for not making any adjustment to the data was based on a visual comparison of 9-month Kaplan-Meier data on OS of patients treated with DTIC in the BRIM-3 trial and those treated with DTIC in the CA184-024 trial, which appeared to show similar OS (MS, Figure 35, p 129).

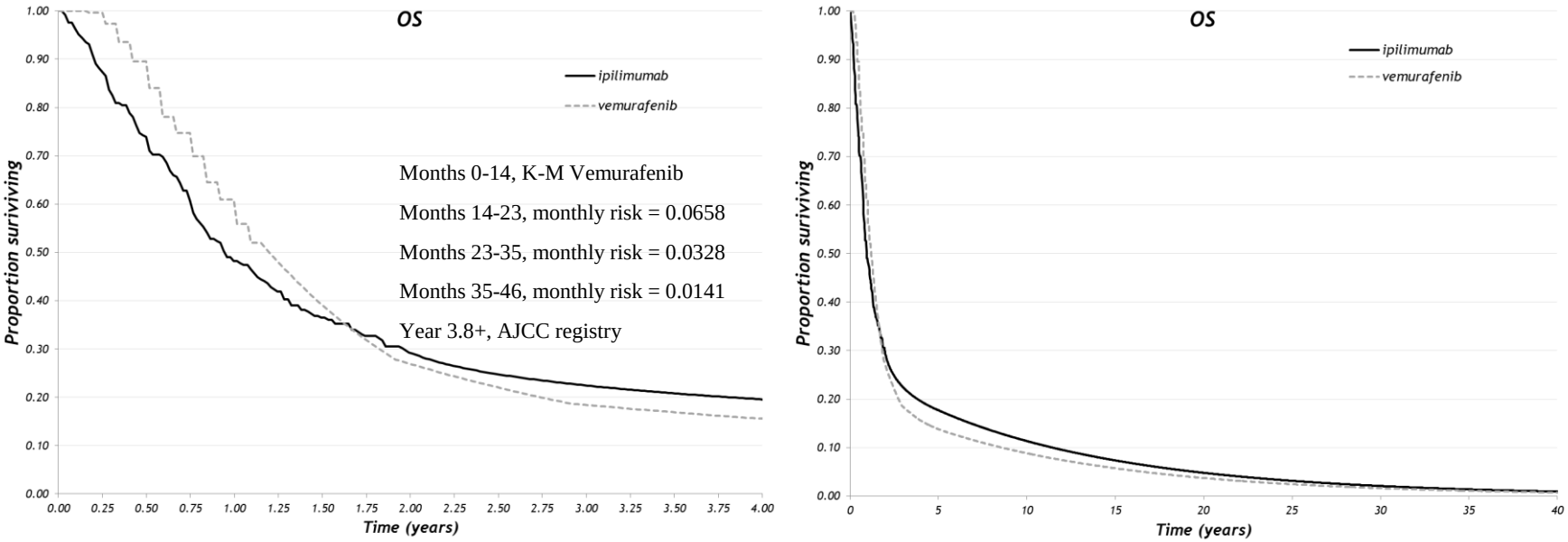
The OS reported in the previous NICE STA submission of vemurafenib (TA269) was used to model first-line vemurafenib.[20] This consisted of Kaplan–Meier data up to 14 months, followed by three different monthly risks of death between months 14 and 46. For patients surviving to month 46, a Weibull distribution was fitted to registry data from year 4 to year 5, while a separate Weibull distribution was fitted to registry data from year 5 onwards. Although the Surveillence, Epidemiology, and End Results (SEER) registry was used in TA269, the manufacturer used the AJCC [Balch 2001] registry data for consistency with ipilimumab and DTIC.

The use of AJCC registry data was in line with the ERG's recommendations in TA269 for the appraisal of vemurafenib. However, the most recent data from the registry reported in Balch 2009 was not used in the model.[41] The manufacturer's rationale for using the registry data reported in Balch 2001[29] instead of the most recent data reported in Balch 2009 was that stage IV data are presented for a longer period (20 years) in the earlier publication whereas it is presented for only 15 years in the later publication. The manufacturer examined the sensitivity of the cost-effectiveness results to the publication date. Using the most recent data, the manufacturer's base-case ICER for ipilimumab compared with DTIC dropped from £16,958 to £14,595 (BRAF V600 mutation-negative), from £31,559 to £26,532 (BRAF V600 mutation-positive), and ipilimumab remained dominant compared with vemurafenib.

Figure 5.4 shows a comparison of the OS curves for vemurafenib compared with ipilimumab. The manufacturer's modelled extrapolation, which uses independent trial arms from BRIM-3 and CA184-024, assumes that vemurafenib has greater OS than ipilumumab in the first 19 months. At this point, the OS curves cross and ipilimumab has greater long-term survival. The implied hazard ratios for ipilimumab compared with vemurafenib in the modelled extrapolation are 1.256 at 1 year, 0.938 between years 1 and 2, 0.883 between years 2 and 3, 0.877 between years 3 and 4, and 0.874 between years 4 and 5, after which equal efficacy is assumed as both treatments use information from registry data.[29]

Although the ERG recognises that there is a lack of head-to-head RCTs comparing ipilimumab with vemurafenib, the ERG notes that the manufacturer did undertake an indirect treatment comparison of ipilimumab and vemurafenib, which was not subsequently used in the economic model (MS, Section 6.7, p 76). The indirect comparison was based on the BRIM-3[7] and CA184-024 trials,[5] which have a common comparator of DTIC. The hazard ratio for ipilimumab 10mg/kg + DTIC from the indirect analysis was 1.16 (95% CI, 0.86, 1.56). Despite having provided an estimate of the hazard ratio from an indirect analysis, the MS does not provide any assessment or discussion on how consistent the results are with the implied modelled extrapolation. This is an important omission given that the use of independent arms from different clinical trials raises concerns about the exchangeability of the populations of the two trials. In particular, the population of the CA184-024 trial comprises both BRAF V600 mutation-positive and -negative patients, while the BRIM-3 trial comprises only BRAF V600 mutation-positive patients. The ERG notes that the manufacturer's choice clearly leads to more favourable outcomes for ipilimumab than using results from the indirect comparison.

Figure 5.4 Overall survival for vemurafenib compared with ipilimumab



5.2.5.2 PFS on first-line therapy

Ipilimumab and DTIC

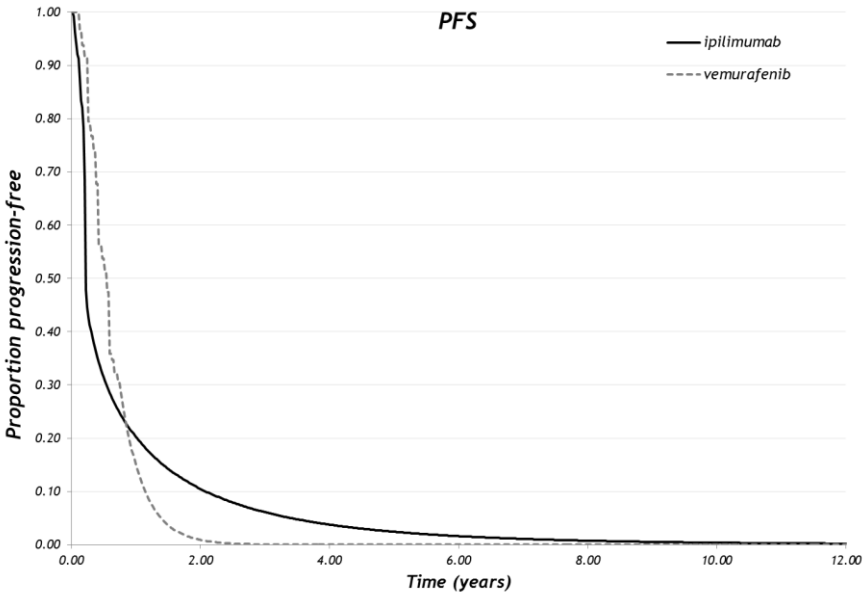
PFS data were used as a proxy to determine the duration of response to first-line treatments, i.e. change to next line of therapy. A similar approach to that used for OS was employed for the extrapolation of PFS data for ipilimumab and DTIC from the CA184-024 trial.[5] A single parametric curve was not sufficient to model the change in hazards over the entire duration of the trial; therefore, a two-part curve fit was employed to extrapolate the data over a lifetime horizon. Kaplan–Meier data for PFS up to 12 weeks were used, which was followed by a Weibull survival function for patients progression-free at week 12. The cut-off point of 12 weeks represents the point at which the hazard changes for patients receiving ipilimumab, which was determined by a visual inspection of the Nelson-Aalen plot. As discussed in the previous section, the ERG considers this approach to be 'purely' statistical and would prefer to see more weight placed on the clinical plausibility of a change in hazard at a particular time point.

Vemurafenib

Time on treatment for first-line vemurafenib was modelled using the data reported in the previous NICE STA submission of vemurafenib (TA269).[20] Kaplan–Meier data for PFS from the BRIM-3 trial was used up to 9 months, which was followed by a monthly risk of progression thereafter. Figure 5.5 shows a comparison of the PFS curves on vemurafenib compared with ipilimumab. The manufacturer's modelled extrapolation, which uses independent arms of the BRIM-3 and CA184-024 trials, assumes that PFS is greater on vemurafenib in the first 9.6 months but after this point, there is a sharp decline in the proportion of patients progression-free on vemurafenib.

Despite having provided an estimate of the hazard ratio of 2.92 for PFS on ipilimumab 10mg/kg + DTIC compared with vemurafenib (MS, Appendix A) from the indirect treatment comparison analysis, the MS does not provide any assessment or discussion on how consistent the results are with the implied modelled extrapolation in Figure 5.5. As noted previously, the manufacturer's choice of using independent treatment arms from different clinical trials is likely to introduce potential bias into the manufacturer's cost-effectiveness results for the comparison of ipilumumab with vemurafenib.

Figure 5.5 PFS curves for ipilimumab and vemurafenib



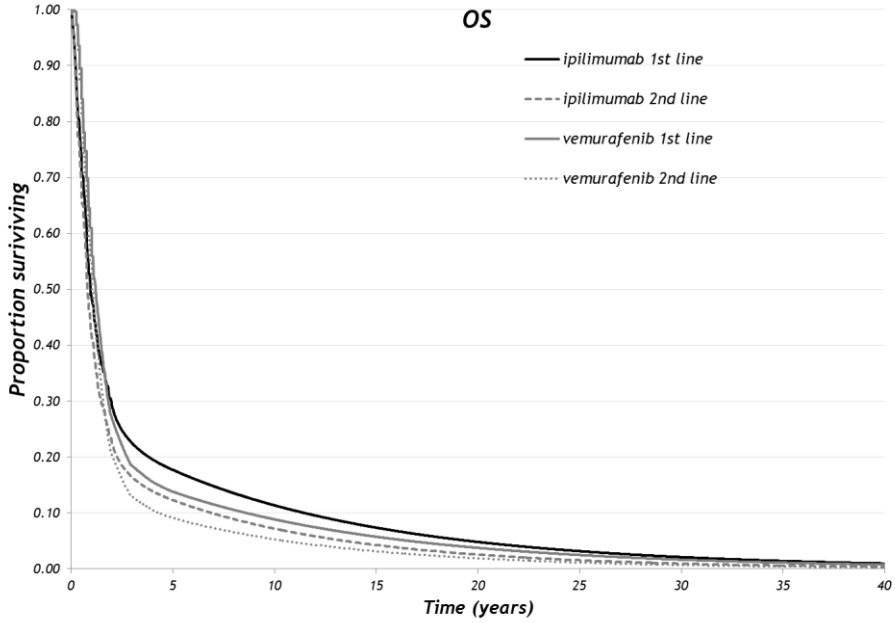
5.2.5.3 OS on second-line therapy

The OS of patients on second-line treatments was based on the first-line OS curves but adjusted downwards by a HR of 1.21 to account for poorer outcomes on second-line treatment. The HR was derived from the expected life years achieved by patients on second-line ipilimumab from TA268.[1] The' goal seek' function in Excel was used to calculate the HR that would produce the same number of second-line life years as TA268 when applied to the first-line OS curve of ipilimumab from the extrapolation of the CA184-024 trial[5] to model second-line ipilimumab. The same HR of 1.21 was applied to the first-line OS curve of vemurafenib in order to generate the OS for second-line vemurafenib. The manufacturer assumed that DTIC would not be given as a second-line treatment; therefore no adjustment was needed to the DTIC curve. Figure 5.6 shows the adjustment to the first-line OS curves for ipilimumab and vemurafenib in order to generate OS curves for those treatments when used second-line.

The ERG considers the approach used by the manufacturer to estimate OS on second-line treatments as quite arbitrary. It is not clear why the manufacturer did not attempt to use the OS for second-line ipilimumab from TA268 directly in the model. In the ERG's points for clarification to the manufacturer, the ERG requested further clarification on the rationale for adopting an alternative approach to estimating OS on second-line therapy when this information was directly available to the manufacturer. In response, the manufacturer stated that the incorporation of the time-dependent OS curves from the previous submission would have been very difficult to implement in the cohort model structure since patients progressed to second line therapy at different time points. Therefore, in order to avoid the additional complexity and uncertainty associated with attempting to model hazards

individually, second line outcomes were implemented as an adjustment to first-line curves.[14] Although the ERG recognises the additional complexity that would be required to implement the curves within a cohort model structure, the ERG notes that the manufacturer could have overcome some of these difficulties by adding a series of sub-health states (tunnel states) to model time to progression explicitly. The ERG would argue that the omission of such health states on the grounds that they would add complexity and additional uncertainty results in a level of uncertainty in its own right, which may introduce potential bias into the manufacturer's cost-effectiveness results.

Figure 5.6 First- and second-line OS curves for ipilimumab and vemurafenib. The first-line curves have been adjusted downwards by a HR = 1.21 to estimate second-line OS



5.2.5.4 PFS on second-line therapy

The duration of response to second-line treatments was derived from the number of pre-progression life years reported in the previous NICE appraisal of ipilimumab (TA268).[1] The mean number of cycles spent pre-progression in the second-line model of ipilimumab was used to generate a constant, per-cycle risk of progression as follows:

$$P(prog) = 1 - e^{(-\frac{1}{D})}$$

where P(prog) is the probability of progression from second-line treatment, and D is the mean duration of response in cycles.

Based on this formula, the mean duration of response of 31.5 weeks (0.604 LYs) in the ipilimumab second-line model (TA268) corresponded to a constant probability of remaining progression-free

equal to 0.969 per weekly cycle. This constant probability was used to model PFS on second-line therapy for ipilimumab.

The duration of response for vemurafenib second-line is unknown. Therefore, in order to derive an estimate for the model, the manufacturer adjusted the median duration of response for vemurafenib reported in BRIM-3 trial (Chapman et al.2011)[7] by the same proportion as second-line ipilimumab. More specifically, the number of pre-progression life years on ipilimumab second line (0.604 LYs) was compared with the number of pre-progression life years on ipilimumab first-line (0.787 LYs) to give a PFS multiplication factor of 0.767 for second-line treatment. This multiplier was then applied to the median duration of response of 5.30 months on vemurafenib from Chapman et al[7] in order to adjust the duration of response on second-line vemurafenib to 4.07 months (17.68 weeks). Using the formula described above the resulting probability of remaining progression-free on second-line vemurafenib was 0.945.

In a similar way to OS, the ERG considers the approach taken by the manufacturer to model progression-free survival on second-line treatments as quite arbitrary. If the manufacturer's preferred choice is to model the sequencing of treatments, then the ERG strongly argues that the additional complexity required to implement the sequencing of treatments must be incorporated into the model using the most appropriate methods. In this case, the analysis would require the direct application of the time-dependent PFS curves for second-line ipilimumab.

5.2.5.5 Best supportive care

BSC is defined as either 'no treatment' or chemotherapy drugs commonly prescribed in the UK, a range of which are used. As reported in the MS, in the base case model, the breakdown of treatments comprising BSC was taken from the MELODY study on the grounds that it contained the largest number of patients (n=220) and additionally is presented as a proportion of patients receiving each treatment rather than a proportion of physicians prescribing each treatment. The median duration of BSC (6.6 weeks) was also taken from the MELODY study and patients were assumed to receive the component drugs for this period.[42, 43] After this time, patients were assumed to not receive any active therapy.

Table 5.3 Breakdown of best supportive care (based upon the MELODY study[28, 44])

Treatment	Proportion of patients
No treatment	69.5%
DTIC	18.8%
Carboplatin	3.6%
Interferon	3.6%
Vindesine	4.5%

5.2.5.6 Treatment sequencing and clinical pathways

As discussed previously, the cost-effectiveness model used in the MS is structured around the sequencing of treatments, where the sequence varies depending on the presence or absence of the BRAF V600 mutation. This differs principally from the model structure used in the MS for ipilimumab in previously treated patients;[1] where there was only one line of active treatment (second line represented BSC). The manufacturer's attempt to model the sequencing of treatments has led to a vast oversimplification of a complex treatment sequencing decision problem. By adopting the approach taken, the manufacturer has been forced to make arbitrary assumptions about overall and progression-free survival on second-line active treatment and third-line BSC.

The treatment pathways allowed for each sub-population, as well as the assumptions used by the manufacturer to populate the model, are discussed separately for BRAF V600 mutation-negative and -positive subgroups below.

BRAF V600 mutation-negative population

Figure 5.7 shows the sequence of treatments for the comparison of ipilimumab with DTIC in the BRAF V600 mutation-negative population. For ipilimumab, only one line of active treatment is modelled; once patients progress on first-line ipilimumab, they move to BSC. For DTIC, two lines of active treatment are modelled; after patients progress on first-line DTIC, they move to second-line treatment with ipilumumab before moving to BSC post-progression. While the ERG is satisfied with the individual treatment pathways for the mutation-negative population, the ERG's main concern relates to the set of assumptions used to model survival on the different lines of treatment. For patients who receive ipilimumab treatment first line, they are assumed to follow the OS curve from the CA184-024 trial[5] up until the point of progression. At the point of progression, which is modelled using the PFS curve from the CA184-024 trial, patients switch to second-line treatment of BSC. At this point, the model assumes that patients continue to follow the OS curve from the CA184-024 trial[5] and remain on BSC until they die (adjusted to account for palliative care which is received 12 weeks prior to death). This implies a sustained benefit of OS from first-line ipilimumab (referred to as '1st line ipi OS' in Figure 5.7). The issue identified by the ERG relates to the contrasting method used to model OS for the comparator treatment. For patients who receive DTIC treatment first line (right hand side of Figure 5.7), they are assumed to follow the OS curve from the DTIC arm of the CA184-024 trial up until the point of progression. At the point of progression, patients are switched to second-line treatment on ipilimumab. The OS for these patients is based on the downward adjustment of the first-line OS curve for ipilimumab (HR = 1.21, as discussed in Section 5.2.5.3). Once patients progress on second-line ipilimumab, they receive third-line BSC. At this point, the model assumes that patients on BSC follow the OS curve of first-line DTIC. The ERG considers this switch between

OS curves on different lines of treatment (particularly second and third line) to be arbitrary and not to be clinically plausible. The different OS curves used to model the different lines of treatment are illustrated in Figure 5.8. No clinical evidence is provided by the manufacturer to support the assumption that patients receiving first-line ipilimumab maintain the sustained benefit of OS in the long-term, while patients receiving second-line ipilimumab (who previously received DTIC) do not maintain the sustained benefit of OS from second-line ipilimumab. The approach used by the manufacturer clearly penalises the comparator treatment, which will inevitably affect the assessment of cost-effectiveness of ipilumumab first line.

In conjunction with the previous discussions in Sections 5.2.5.3 and 5.2.5.4 for the estimation of OS and PFS on second-line treatment, the switching of OS curves between lines of treatment is a major concern to the ERG and calls into question the validity of the treatment sequencing approach employed by the manufacturer. The implications of the assumptions about OS on different lines of treatment are explored by the ERG in Section 6.

Figure 5.7 Treatment sequences for BRAF V600 mutation negative patients; ipilimumab vs DTIC

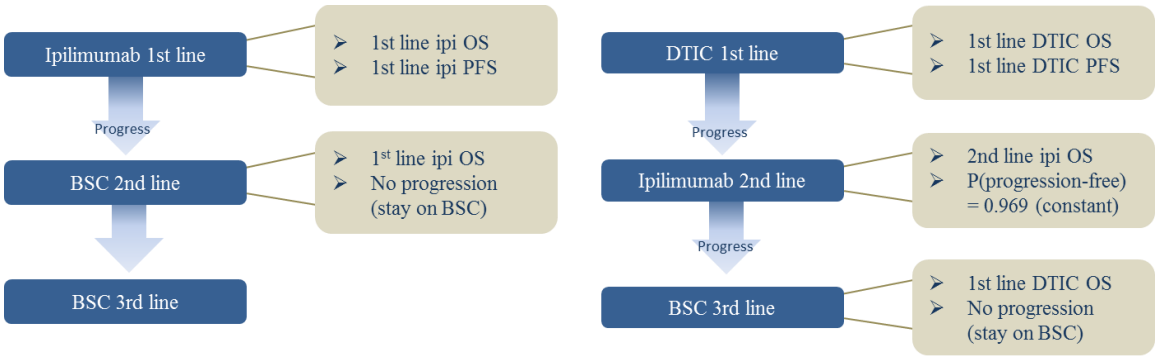
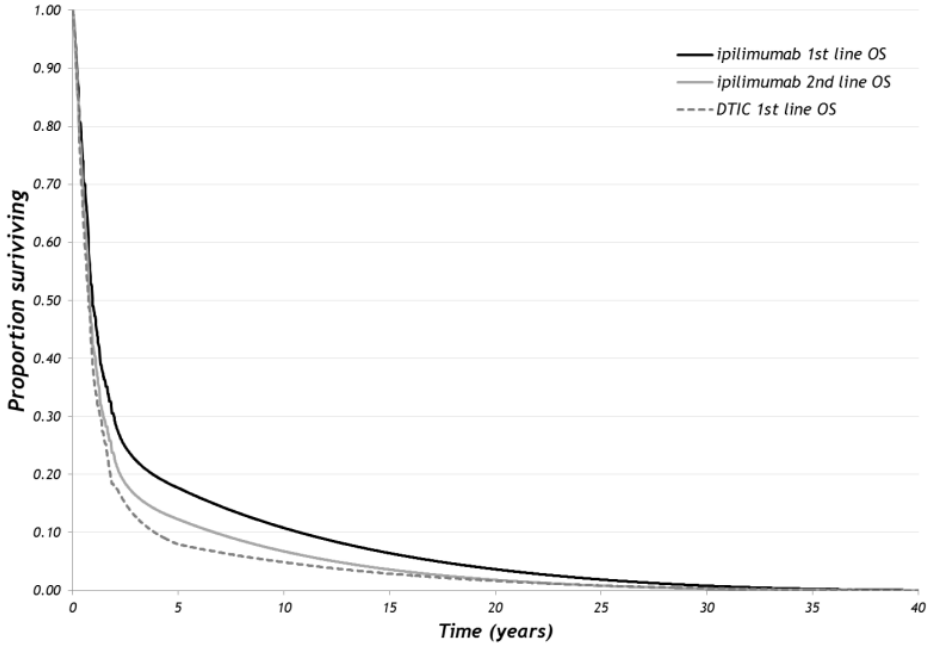


Figure 5.8 Relative effectiveness in terms of OS of ipilimumab first line, ipilimumab second line and DTIC first line



BRAF V600 mutation-positive population

Figure 5.9 shows the sequence of treatments for the comparison of ipilimumab with DTIC in the BRAF V600 mutation-positive population, while Figure 5.10 shows the comparison of ipilimumab with vemurafenib in the same population.

Figure 5.9 Treatment sequences for BRAF V600 mutation positive patients for ipilimumab compared with DTIC

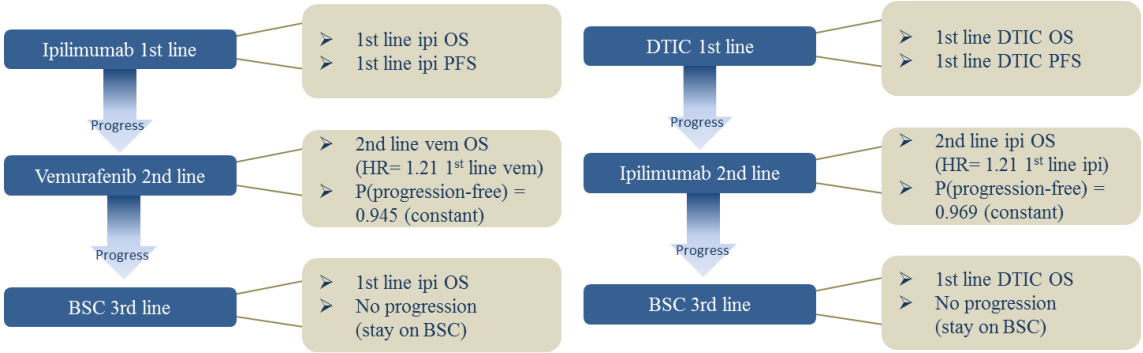
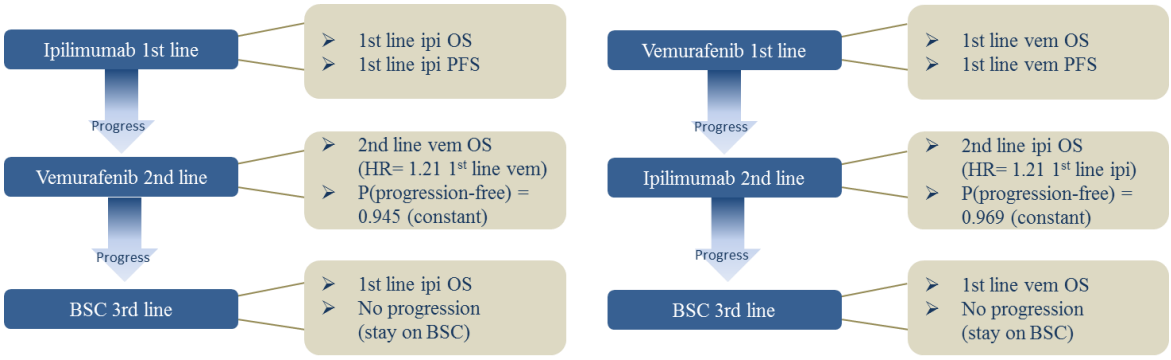
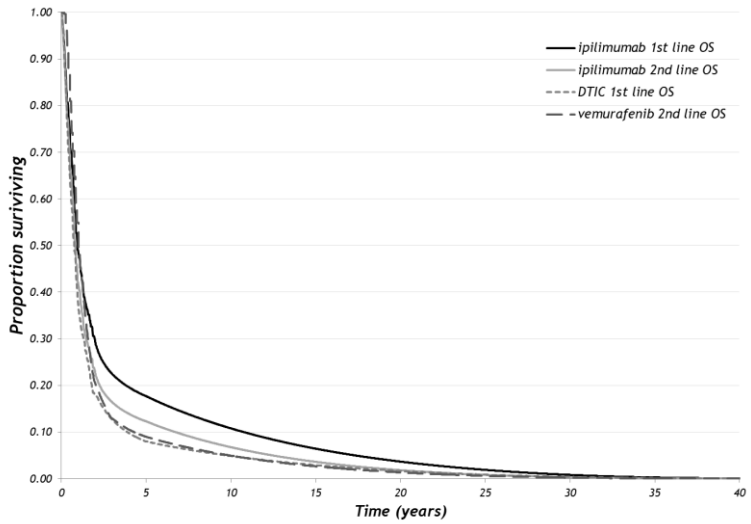


Figure 5.10 Treatment sequences for BRAF V600 mutation positive patients for ipilimumab compared with vemurafenib



The modelled treatment pathways for mutation-positive patients show similar inconsistencies in terms of the way that OS is modelled in the treatment sequence as the mutation-negative population. For the comparison of ipilimumab with DTIC (Figure 5.9), patients who receive ipilimumab treatment first line follow the OS curve from the CA184-024 trial up to the point of progression.[5] At the point of progression, which is modelled using the PFS curve from the CA184-024 trial, patients switch to second-line treatment on vemurafenib. At this point, patients follow the OS curve for second-line vemurafenib, which is based on a downward adjustment of the first-line vemurafenib curve from the BRIM-3 trial. When patients progress on second-line vemurafenib, they are switched to third-line BSC. At this point, patients who survive are assumed to follow the OS of first-line ipilimumab without any downward adjustment to the first-line OS curve. The ERG considers this switch to ipilimumab first-line OS after progression on vemurafenib second line to be difficult to justify and unlikely to be supported by clinical evidence. The different OS curves used to model the different lines of treatment are illustrated in Figure 5.11. From this figure it is clear that the approach used by the manufacturer to model OS on the different lines of treatment greatly favours ipilumumab in terms of overall survival compared with DTIC.

Figure 5.11 Relative effectiveness in terms of OS of ipilimumab first line, ipilimumab second line, DTIC 2st line and vemurafenib second line



Similarly, for the comparison of ipilimumab with vemurafenib (Figure 5.10) patients who receive vemurafenib treatment first line follow the OS curve from the BRIM-3 trial up until the point of progression.[7] At the point of progression, which is modelled using the PFS curve from BRIM-3, patients switch to second-line treatment on ipilimumab. The OS for these patients was based on the downward adjusted OS curve for ipilimumab from the CA184-024 trial.[5] When patients progress on second-line ipilimumab, they move to third-line BSC. At this point, the model assumes that patients who survive now follow the OS curve of first-line vemurafenib. Again, the ERG notes the unfounded assumption that OS on BSC arbitrarily equates to that of first line treatment despite a switch to a different active treatment before progression to BSC.

5.2.5.7 Background mortality

Along with the melanoma-specific mortality rates across treatments, an additional age-specific background mortality rate was incorporated in the model while the registry data hazards were active. These were based on Interim Life Tables for England and Wales (2009-2011)[45] using a weighted average of male and female mortality risks derived from the gender distribution of participants in the CA184-024 trial.[5]

5.2.5.8 Adverse events

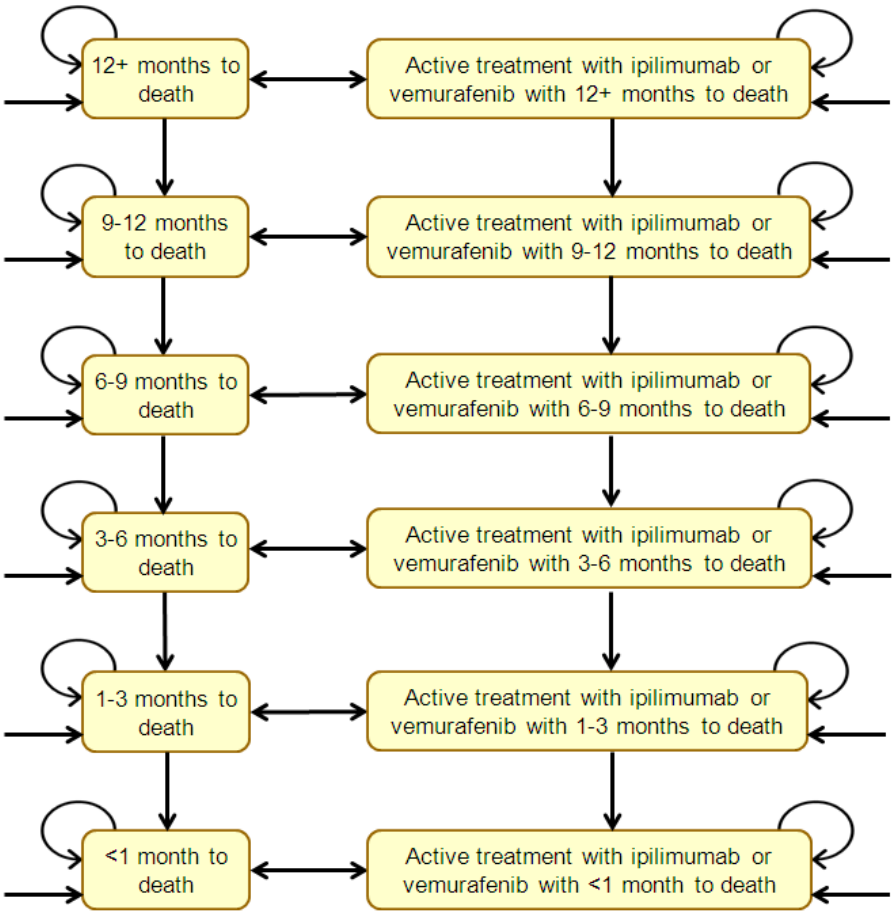
The inclusion criteria for adverse events in the model were any grade 3+ event, or grade 2+ for diarrhoea, with an incidence greater than or equal to 3%. In addition, all endocrine disorders were included as these are known to be a serious event associated with treatment with ipilimumab. The incidence of adverse events for patients treated with ipilimumab was taken from the CA184-024 trial, [5] while the incidence for vemurafenib was from Chapman et al.[7] Based on data from patients treated

with DTIC in the CA184-024 trial, no events met the inclusion criteria. As a result, the incidence of all adverse events was set to 0% for these patients. The modelling of the HRQoL and costs of adverse events are discussed in detail in sections 5.2.6 and 5.2.7.4.

5.2.6 Health-related quality of life

Health-related quality of life (HRQoL) outcomes were quantified within the cost-effectiveness model by using sub-health states based on time to death, which capture patients' HRQoL as a function of how much lifetime they have left before death (Figure 5.12). The approach used by the manufacturer differs from that used in typical cancer models, where HRQoL is usually reflected by assigning utility values to the pre-progression and post-progression health states. The manufacturer argued that the trial data (both the CA184-024[5] and MDX010-20 trials[18]) suggested that progression-based utility estimates may not be sufficiently predictive to accurately account for HRQoL in this indication.

Figure 5.12 Sub-health states used to model HRQoL for ipilimumab and vemurafenib treatment (Figure 27, P115 in the MS)



In the absence of EQ-5D data, the manufacturer used HRQoL data that were collected in the CA184-024 trial using the EORTC QLQ-C30 questionnaire.[5, 30] The valuation algorithm by Rowen et al[31] was used to derive utility values from the EORTC QLQ-C30 in order to inform the assessment of cost-

effectiveness. The ERG has some concerns that no direct EQ-5D data were used in the model and that the algorithm by Rowen et al may not be sufficiently generalisable to this patient population as it is based upon a dataset from an international study of patients with multiple myeloma with the valuation study being carried out in the UK.

The utility values used in the MS were said to be consistent with the utilities used in the second-line submission of ipilimumab (TA268);[1] however the ERG notes that the utility values in TA268 were based on progression and not on proximity to death. The manufacturer's rationale for using time-dependent utilities was based on the analysis of patient-level HRQoL data from the CA184-024 trial, which showed a strong correlation between HRQoL and time-to-death.[5] In addition, the approach allowed a utility decrement for active treatment with ipilimumab to be incorporated within the analysis. This decrement was assumed to represent the impact of treatment-related adverse events on HRQoL. In the absence of evidence for vemurafenib, the manufacturer assumed that the same decrement could be applied to vemurafenib on the basis that the number of patients experiencing grade 3+ adverse events was similar. The manufacturer also assumed that the utility values at each time point before death for vemurafenib were identical to those of ipilimumab. To assess the validity of this assumption, the ERG requested additional clarification from the manufacturer. In response, the manufacturer stated that this assumption was necessary as (i) no data were available for vemurafenib; (ii) the number of serious adverse events (SAEs) for patients treated with ipilimumab and vemurafenib were not significantly different; and (iii) the long-term impact of adverse events is likely to be greater with vemurafenib as it is continuously dosed whereas ipilimumab is not.[14]

Superseded – see Erratum

The utility weights used in each sub-health state in the manufacturer's model are summarised in **Error! Reference source not found.**Table 5.4. The utility estimates were applied to the proportion of patients within each sub-health state during each cycle of the model, in order to estimate QALYs for each treatment strategy.

Table 5.4 Summary of utility values used for the cost-effectiveness analysis (adapted from Table 49, P157 in the MS)

Time to death	Utility value (95% CI)	Justification
<1 month	0.631 (0.600 – 0.668)	Best fit to trial data
Months 1-3	0.739 (0.710 – 0.768)	Best fit to trial data
Months 3-6	0.810 (0.780 – 0.840)	Best fit to trial data
Months 6-9	0.854 (0.823 – 0.885)	Best fit to trial data
Months 9-12	0.880 (0.847 – 0.912)	Best fit to trial data
Months 12+	0.885 (0.853 – 0.917)	Best fit to trial data
Treatment effect of ipilimumab (utility decrement)	-0.021 (-0.042 – 0.001)	Best fit to trial data
Treatment effect of vemurafenib (utility decrement)	-0.021 (-0.042 – 0.001)	Assumed the same based upon grade 3+ event rates

A key concern for the ERG is that the health state utility values only capture the decline in HRQoL close to death and adverse effects associated with treatment but do not capture a positive impact on HRQoL from treatment. The ERG has a number of other concerns with the approach and assumptions used by the manufacturer, which are discussed below.

5.2.6.1 The source of HRQoL data

The CA184-024 clinical study was the only source of HRQoL data used to inform the model.[5] Although the manufacturer performed a systematic review to identify utility and HRQoL studies for advanced (unresectable or metastatic) melanoma, the results were not subsequently used in the model. Thirteen studies were identified that report relevant HRQoL data and seven of the studies directly measured quality of life. These utility values are summarised in Table 5.5. However, the utility values identified in the systematic review were not used to inform the model or examined in any sensitivity analysis by the manufacturer. The ERG explores the implications of using utility values for pre-progression and post-progression as used in TA268[1] in Section 6.

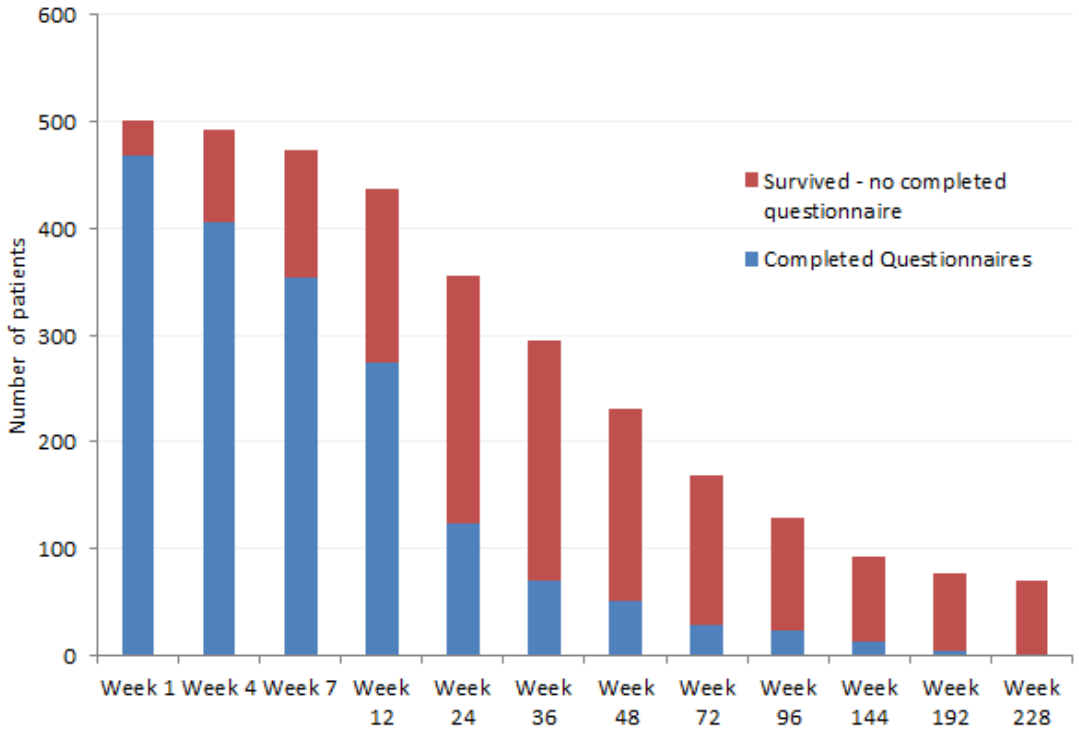
Table 5.5 Summary of literature utilities from the MS systematic review of primary utility studies in advanced melanoma (Table 47, P154 in the MS)

Publication	Utilities	n	Source
Askew 2011[46]	0.85 stage III 0.86 stage IV	100 102	EQ-5D
Batty 2011[47] (previously treated ipilimumab)	0.80 pre-progression 0.76 post progression	971	EORTC-8D
Batty 2012[48] (previously treated ipilimumab)	0.80 pre-progression 0.76 post progression 0.64 pre-progression 0.62 post progression	971 963	EORTC-8D SF-6D
Beusterien 2009[49]	0.85 PR, 0.77 SD, 0.59 PD & BSC	140, 63 UK	SG Vignettes (UK)
Dixon 2006[50]	0.77 (3 months) to 0.87 (48 months)	80 to 10	EQ-5D
Hogg 2010[51]	0.84 PR, 0.79 SD, 0.55 PD, 0.54 BSC	87	SG Vignettes (Canada)
King 2011[52]	0.53 stage III new diagnosis 0.91 stage III established diagnosis 0.69 stage IV new diagnosis 0.53 stage IV established diagnosis	8 10 11 24	Time trade-off by patients

5.2.6.2 HRQoL values

The EORTC QLQ-C30 questionnaire was collected in the CA184-024 clinical study at weeks 1, 4, 7 and 12 of the induction phase of treatment, and weeks 24, 36 and 48 of the maintenance phase and subsequent weeks during follow-up.[5] According to the MS, baseline questionnaires (week 1) were completed by 477 patients, while completion rates at subsequent time points decreased steadily; there were 52 completed questionnaires at week 48 and this dropped to only 1 completed questionnaire in week 228. The number of completed EORTC QLQ-C30 questionnaires at different time points in the CA184-024 clinical study and the number of patients who had survived at each week but had not completed a questionnaire are depicted in Figure 5.13.

Figure 5.13 EORTC QLQ-C30 completed questionnaires and survived patients who had not completed questionnaires at weeks 1 to 228 in CA184-024



The ERG has some concerns that the progressively lower completion rates of EORTC QLQ-C30 questionnaires amongst surviving patients at subsequent points in time may be associated with selection bias. The ERG requested further clarification on the breakdown of reasons for non-completion of the EORTC QLQ-C30 questionnaire by treatment and at each time point; however the manufacturer could not provide such information since this data were not captured in the case report form for the trial.[14]

5.2.7 Resource use and costs

The MS gave a detailed description of resource use and costs incurred over time. These included: drug acquisition costs; drug administration costs; costs of second and third-line treatment; and adverse events costs. The MS model adopted an NHS and PSS cost perspective. For the identification of ipilimumab administration costs, since there are no HRG and PbR codes specific to ipilimumab, the manufacturer used existing chemotherapy delivery HRGs to cost its administration. In addition, the manufacturer performed a systematic literature review to identify cost and resource use studies for advanced (unresectable or metastatic) melanoma; five studies met all the inclusion criteria.

5.2.7.1 Drug acquisition costs

The dose of ipilimumab per administration was calculated based on individual patient level data for the weights of UK patients from the CA184-024 clinical trial[5] (n=40) and the ipilimumab

compassionate use program (n=258). The mean number of vials per patient for each dose of ipilimumab was 5.23, which was similar to the mean number of vials in the submission of ipilimumab for previously treated patients (5.21).[1] The number of ipilimumab administrations in the CA184-024 trial was dependent on the number of adverse events in the induction period; therefore not all patients received all 4 induction doses of ipilimumab. The proportion of patients receiving each dose during the induction phase of the trial was used within the model to predict how many patients would receive each dose in clinical practice. The number of patients receiving subsequent re-inductions was estimated from the MDX010-20 clinical trial.[18] The proportions of patients receiving each of the 4 possible doses within the re-induction phase were assumed to be the same as the proportions of patients receiving each of the 4 possible doses during the initial induction. Table 5.6 shows the proportions of patients receiving each dose in the model. The total drug cost per administration of ipilimumab is [redacted] (Table 5.7).

Table 5.6 Proportion of patients receiving induction and re-induction doses of ipilimumab

Induction Number	% of Patients Receiving Induction	% of Patients Receiving Dose				
		Dose 1	Dose 2	Dose 3	Dose 4	Mean Doses Received
Induction 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
				Mean number of doses received:		[redacted]

The costs of vemurafenib were sourced from the previous NICE appraisal of vemurafenib (TA269).[20] Patients were assumed to be dispensed with 4 packs of vemurafenib tablets every 4 cycles. The total drug cost per administration of vemurafenib is [redacted] (Table 5.7).

The cost of DTIC and BSC was based on the dosing schedules from the product SPCs.[36, 38, 43] An average height and weight for patients of 170cm and 78.65kg, respectively, were assumed based upon the characteristics of patients in the CA184-024 clinical trial.[5] The drug costs for all treatments are summarised in Table 5.7. Drug prices were sourced by the manufacturer from the BNF (September 2013)[34] and the Electronic Market Information Tool (eMIT, October 2013),[33] including a patient access scheme (PAS) for both ipilimumab and vemurafenib.

Table 5.7 Drug dosages required and drug cost per administration studies (Table 54, P167 in the MS)

Drug	Total dose required	Method used	Total drug cost per administration
Ipilimumab	5.23 vials	Method of moments	5.23 * [redacted] = [redacted]
Vemurafenib*	4 packs	4 packs dispensed every 4 cycles	4 * [redacted] = [redacted]
DTIC	2 x 1000mg vials	Round up to nearest full vials	2 * £26.94 = £53.88
Best supportive care			
DTIC	2 x 1000mg vials	Round up to nearest full vials	2 * £26.94 = £53.88
Paclitaxel	1 x 300mg vial + 2 x 30mg vials	Round up to nearest full vials	£22 + 2*£4 = £30.00
Carboplatin	1 x 150mg vial + 2 x 50mg vials	Round up to nearest full vials	£10 + 2*£5 = £20.00
Paclitaxel and carboplatin	As above for the separate components	Round up to nearest full vials	£30 + £20 = £50.00
Cisplatin	1 x 100mg vial + 1 x 50mg vial	Round up to nearest full vials	£14 + £7 = £21.00
Interferon alfa-2b	1 x 10MU vial	Round up to nearest full vials	£42.35
Cisplatin and interferon	1 x 50mg cisplatin vial + 1 x 10MU interferon vial	-	£7 + £42.35 = £49.35
Vindesine	2 x 5mg vials	Round up to nearest full vials	2 x £78.30 = £156.60
Treosulfan	1 x 5000mg vial + 1 x 1000mg vial	Round up to nearest full vials	£39.44 + £152.41 = £191.85

*vemurafenib costs are provided per dispensation

5.2.7.2 Drug administration costs

Drug administration costs were calculated by the manufacturer for all treatments, with unit costs being sourced from the NHS Reference costs 2011/2012.[32] For all parenteral drugs (ipilimumab, DTIC and the majority of the drugs which make up BSC) administration was assumed to be carried out as a day case appointment, applying the maximum cost for parenteral chemotherapy to each administration. The administration costs of vemurafenib were applied as an outpatient appointment for the first cycle only, as subsequent doses were assumed to be taken orally at home. The SPC for ipilimumab indicates that liver and thyroid function tests should be performed prior to each dose being administered; the additional cost of a single complete metabolic panel was added to the administration cost of ipilimumab.

Two types of resource use costs were additionally included within the model: (i) one off costs, which included treatment initiation, progression to a new line of therapy, and terminal care costs applied on death; and (ii) per cycle costs, which included on treatment costs and receiving palliative care. Based on the systematic literature review to identify cost and resource use studies for advanced (unresectable or metastatic) melanoma, the manufacturer used the MELODY study[43] for applying resource use

costs. The costs are presented within the MS (Table 58, P170 in the MS). The expected use of each item of resource was applied within the model to generate the total cost of the aggregated resource use per cycle (Table 59, P172 in the MS).

5.2.7.3 Costs associated with second and third-line treatment

The costs of second-line treatment with ipilimumab were taken from the second-line submission (TA268),[1] with the PAS included. An average drug cost per cycle for second-line ipilimumab was included within the model. This was based on the total drug costs in the second-line model ([redacted]) and on the number of pre-progression life years (0.604 LYs), which corresponds with a mean duration of response of 31.5 weeks. The average cost of second-line ipilimumab per cycle was calculated as [redacted]/31.5 = [redacted]. This was then adjusted proportionately to account for the difference in average weight between the CA184-024 clinical trial[5] and the second-line trial using a multiplier of 0.9977, which generated a per cycle drug cost of [redacted] for second-line ipilimumab.

In order to explore the implications of using a cost per cycle in the model for second-line ipilimumab, whereas a cost per dose was used for first-line ipilimumab, the ERG conducted an exploratory analysis to estimate the average cost of first-line ipilimumab per cycle, as used in the model. The total drug costs of first-line ipilimumab were [redacted] based on the proportion of patients who received each dose and were eligible to receive re-induction doses (see Table 5.8). The number of pre-progression life years for first-line ipilimumab in the model is 0.626, which corresponds with a mean duration of response of 32.6 weeks. This results in an average cost of first-line ipilimumab per cycle of [redacted]/32.6 = [redacted], which represents a 42% difference in the drug cost of ipilimumab per cycle between second-line and first-line treatment ([redacted] vs. [redacted]). The disparity in the drug costs of ipilimumab between first- and second-line is not discussed in the MS. The ERG recognises that the total costs first- and second-line will differ depending on the different proportions of patients receiving treatment but the ERG does not believe that there is any clinical reason why the acquisition cost of the drug per cycle in the model should differ between first- and second-line treatments. This is likely to be a key driver of the cost-effectiveness results, especially since the model is structured around the sequencing of treatments where the comparator treatment is likely to receive higher costs per cycle of ipilumumab as it is given as a second-line therapy. The implications of the cost difference are explored within the additional analyses undertaken by the ERG in Section 6.

Table 5.8 First line treatment costs of ipilimumab

Weeks	Proportion of patients pre-progression 1st line ipilimumab	% patients receiving dose	Proportion of patients receiving Ipilimumab	Ipilimumab 1st line drug costs
1	0.944	[redacted]	[redacted]	[redacted]
4	0.827	[redacted]	[redacted]	[redacted]
7	0.750	[redacted]	[redacted]	[redacted]
10	0.682	[redacted]	[redacted]	[redacted]
13	0.393	[redacted]	[redacted]	[redacted]
16	0.343	[redacted]	[redacted]	[redacted]
19	0.321	[redacted]	[redacted]	[redacted]
22	0.295	[redacted]	[redacted]	[redacted]
25	0.276	[redacted]	[redacted]	[redacted]
28	0.252	[redacted]	[redacted]	[redacted]
31	0.229	[redacted]	[redacted]	[redacted]
34	0.208	[redacted]	[redacted]	[redacted]
37	0.199	[redacted]	[redacted]	[redacted]
40	0.180	[redacted]	[redacted]	[redacted]
43	0.181	[redacted]	[redacted]	[redacted]
46	0.176	[redacted]	[redacted]	[redacted]
			TOTAL:	[redacted]

For second-line vemurafenib, the drug costs in the MS were applied using the cost per mg, with the PAS included.[20] To account for the wastage incorporated in the "cost per dispensation" cost, an additional 5.78% was added to the drugs costs. The total drug cost per cycle for second-line vemurafenib was [redacted]. The ERG performed an exploratory analysis to compare first- and second-line costs per cycle of vemurafenib. The cost per cycle on vemurafenib first-line was [redacted]. There is a marginal cost difference for vemurafenib between the two lines of treatment, which is not as significant as that for ipilimumab and therefore less of a concern to the ERG.

The drug and administration costs for BSC were applied within the model only to patients in the first 7 cycles of BSC, based on the median duration of 6.6 weeks for treatment from the MELODY study.[28, 43]

5.2.7.4 Costs of adverse events

Costs of adverse events for ipilimumab and comparators was based on additional cost data from NHS reference costs and from the Oxford Outcomes report, inflated to 2012 prices using PSSRU inflation indices.[35] Table 5.9 summarises the adverse events and their respective costs that were included in the economic model. The costs of endocrine disorders were assumed to be incurred once every 6 months, as this is an on-going condition. The costs for all other events were applied once at treatment initiation.

Table 5.9 List of adverse events and summary of costs included in the economic model (Table 63, P177 in the MS)

Adverse events	Average cost		Reference
	Ipilimumab	Vemurafenib and BSC	
Myalgia/Pain	£146.00	£146.00	HRG service code: 191, Pain management, multi-professional non-admitted face-to-face
Skin Reaction	£245.99	£245.99	Oxford Outcomes: Average of Rash and Pruritus
Fatigue	£173.89	£173.89	Oxford Outcomes: Fatigue
Hypotension	£0.00	£0.00	*
Diarrhea (not including colitis)	£684.01	£511.49	Oxford Outcomes: Diarrhoea
Colitis	£853.10	£983.36	Oxford Outcomes: Colitis
Dyspnoea	£0.00	£0.00	*
Resp. Distress/ Pulm. Edema	£1,950.00	£1,950.00	DZ20Z, Pulmonary Oedema, NHS Trusts Non-Elective Inpatient (Long Stay) HRG Data
Anaemia	£728.62	£792.10	Oxford Outcomes: Anaemia
Neutropenia	£920.13	£612.08	Oxford Outcomes: Neutropenia
Endocrine disorders	£473.72	£563.91	Oxford Outcomes: Hypopituitarism - every 6 months
Arthralgia	£146.00	£146.00	HRG service code: 191, Pain management, multi-professional non-admitted face-to-face

*The following adverse events were not included in the Oxford Outcomes Report because physicians indicated that they would not be common and/or costly: headache, pain, injection site reaction, leucopoenia, hypotension, hypertension, dyspnoea, stomatitis, urticaria, vitiligo, anuria, oliguria, and peripheral neuropathy. Costs for these have therefore been set to zero.

5.2.8 Cost-effectiveness results

5.2.8.1 Base-case

The manufacturer presented results for the base-case analysis for both the BRAF V600 mutation-positive and -negative sub-populations using ipilimumab data from either the CA184-024 trial[5] or the pooled chemotherapy-naïve dataset.[53] Since the manufacturer's results from both datasets appeared to be consistent, the results based on the CA184-024 trial are presented below. The manufacturer undertook pair-wise comparisons of ipilimumab with DTIC and ipilimumab with vemurafenib in the mutation-positive population, while ipilimumab was compared with DTIC in the mutation-negative population. Tables 5.10-5.11 present the manufacturer's base-case results.

For BRAF V600 mutation-positive patients, treatment with ipilimumab was found to dominate vemurafenib, while the incremental cost-effectiveness ratio (ICER) for the comparison with DTIC was £31,559. For mutation-negative patients, the ICER for ipilimumab compared with DTIC was £16,958.

Table 5.10 Base case results, CA184-024 data for ipilimumab – BRAF V600 mutation-positive

Incremental pair-wise comparison with ipilimumab

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. baseline (A)	Incremental analysis
DTIC	£44,267	1.56				
Ipilimumab	£68,033	2.31	£23,766	0.75	£31,559	£31,559
Vemurafenib	£80,658	2.13	£12,625	-0.18	£63,534	Dominated

Table 5.11 Base case results, CA184-024 data for ipilimumab – BRAF V600 mutation-negative

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) Ipi vs. comparator
Ipilimumab	£57,760	3.3522	2.3527			
DTIC	£44,267	2.1476	1.5570	£13,492	0.7957	£16,958

5.2.8.2 Sensitivity analyses

Deterministic sensitivity analysis

Superseded – see Erratum

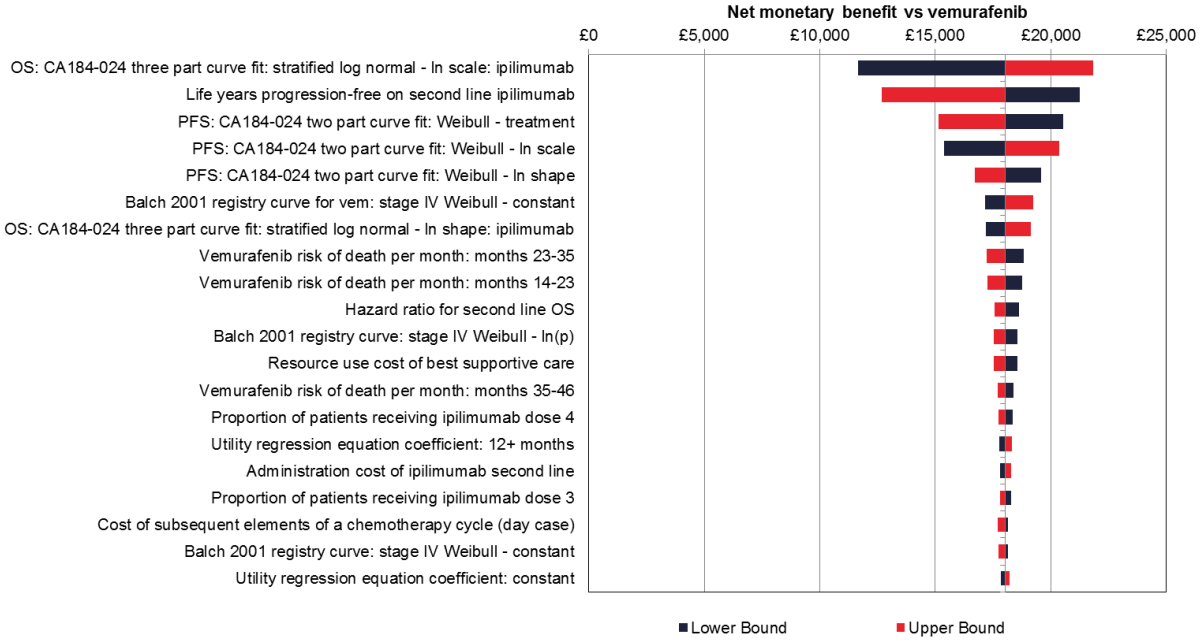
The manufacturer presented a series of one-way deterministic sensitivity analyses (DSA) to assess the impact of uncertainty on key input parameters on the ICERs. The manufacturer only presented sensitivity analyses for the BRAF V600 mutation-positive population since the ICER for ipilumumab compared with DTIC in the BRAF V600 mutation-negative population was lower than in the BRAF V600 mutation-positive population; therefore the sensitivity analyses for the mutation-positive population was assumed to represent a worst case scenario.

Figure 5.14 shows a tornado diagram of the 20 parameters which the manufacturer deemed to be the most influential parameters on the assessment of cost-effectiveness for ipilimumab compared with vemurafenib. The parameters were varied between their upper and lower bounds and the effect on incremental net benefit was presented. The manufacturer used two different willingness to pay thresholds for the calculation of incremental net benefit; £30,000 per QALY for the comparison with vemurafenib and £50,000 per QALY for the comparison with DTIC. It is not clear to the ERG why the manufacturer would present the cost-effectiveness results for the different comparisons using different cost-effectiveness thresholds. The ERG notes that the use of the higher threshold for the comparison with DTIC will make ipilimumab appear to have a higher probability of being cost-effective.

According to the manufacturer's DSA, the model proved to be most sensitive to the parameters used to model overall survival of ipilimumab and DTIC, the time spent on second-line treatment and the time spent on first-line treatment with ipilimumab relative to DTIC.

Figure 5.14 Tornado diagram containing 20 most influential parameters vs. Vemurafenib

CA184-024 data for ipilimumab



Probabilistic sensitivity analysis

Superseded – see Erratum

The manufacturer performed probabilistic sensitivity analysis using 1,000 simulations. Scatter plots and cost-effectiveness acceptability curves were presented in the MS. The manufacturer's PSA concluded that the probability of ipilimumab being the most cost-effective treatment compared with DTIC was 96% at a willingness to pay threshold of £50,000. However, as noted above, it is not clear to the ERG why the manufacturer used a threshold of £50,000 for the comparison with DTIC. At a threshold of £30,000 per QALY, the probability that ipilimumab is cost-effective is 40%.

The mean ICERs that were derived from the probabilistic sensitivity analysis were similar to those of the deterministic analysis as shown in Table 5.12.

Table 5.12 Results of PSA (mean over 1,000 runs) (Table 78, P199 in the MS)

Ipi data source	Ipilimumab		Vemurafenib		DTIC		ICER vs. vem	ICER vs. DTIC
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
CA184-024	£67,938	2.29	£80,629	2.12	£44,298	1.54	Dominated	£31,619
Pooled chemo-therapy-naïve	£68,736	2.38	£78,156	2.08	£42,898	1.54	Dominated	£30,756

5.2.8.3 Scenario analyses

The MS also included a series of scenario analyses that were performed to check the robustness of the model to uncertainty related to structural assumptions, e.g. time horizon, treatment pathway, approach to modelling drug dosing, utilities and treatment efficacy assumptions. The main analyses are reported

in Table 79 of the MS (p 200-202). The results of the manufacturer's scenario analyses showed that the cost-effectiveness of ipilimumab was found to be relatively insensitive to changes in the chosen structural assumptions including the source of clinical data and assumptions regarding the modelling of survival. The manufacturer states that none of the variations made to the base-case analysis resulted in an ICER that was no longer considered cost-effective. The least favourable ICER for ipilimumab was £49,579 vs. DTIC, which assumed a single parametric curve fit to overall survival data using a lognormal distribution.

From the list of scenarios undertaken by the manufacturer, the ERG considers the scenario, 'no active second-line treatments 'as the most important. This scenario only considers OS and PFS on first-line treatment, i.e. it represents a three-state model for pre-progression, post-progression and death. The only second-line therapy considered is that of BSC. The resulting ICER for the comparison of ipilimumab with DTIC increased from £31,559 to £42,449, while the ICER for the comparison with vemurafenib was no longer dominant and became £28,980 in the BRAF V600 mutation-positive population. The implications of the manufacturer's choice of model structure are explored in more detail by the ERG in Section 6.

5.2.9 Model validation

The approach used by the manufacturer was stated to be validated by 3 leading external health economists, who were selected as key opinion leaders practicing in the UK. The model was presented to the health economists during interviews and their opinions were used in order to determine the model base case in terms of survival analysis and quality of life. The external health economists did not verify the accuracy of the implementation of the model; this was conducted via the manufacturer's internal quality control processes.

The manufacturer states that clinicians were not consulted specifically for this submission; however, clinicians were consulted regarding specific topics (time horizon, survival analysis, dosing and adverse events) as part of the ipilimumab submission for previously treated patients (TA268).[1]According to the manufacturer, the input from these clinicians was used to inform the methods for survival analyses, dosing and application of adverse events in the current submission. The ERG believes that input from clinicians for the current ipilimumab submission would have been invaluable given the alternative approach used by the manufacturer, which attempts to model the sequencing of treatment. In particular, clinical validation of the assumptions required to model overall survival on different lines of treatment would have been very useful.

For HRQoL, the manufacturer states that the utility values used in the model were similar to those identified in the systematic search that was performed, suggesting that they were consistent with those typically associated with a malignant melanoma population. The utility values used were also stated to

be similar to the values used in the economic model for the appraisal of second-line ipilimumab (TA268),[1] which were validated by clinicians. However, the ERG notes that no scenarios were presented by the manufacturer to demonstrate this consistency and the approach taken to model HRQoL differs greatly from that used in TA268[1] by using time-dependent instead of progression-based utility values. The implications on the cost-effectiveness results have not been explored by the manufacturer.

Furthermore, the manufacturer has not validated the use of independent treatment arms from different clinical trials (CA184-024[5] for ipilimumab and DTIC, and BRIM-3[7] for vemurafenib) for the assessment of cost-effectiveness of ipilimumab compared with vemurafenib. The generalisability of the CA184-024 clinical study to the UK population has only been briefly discussed by the manufacturer, which states that it is generally comparable to the UK population receiving first- line therapy as reported in Lorigan et al (2013),[43] but that the trial population may be slightly more severe.

5.3 Summary of uncertainties and issues from the cost-effectiveness analysis

The ERG considered the manufacturer's economic submission to meet the requirements of the NICE reference case. However, the ERG does not consider the economic model structure appropriate to address the decision problem in light of the lack of evidence available on the sequencing of treatments for previously untreated malignant melanoma. Although the structure of the model is not wholly appropriate for the evidence base that is available for first-line ipilimumab, it is possible to 'turn off' the treatment sequencing part of the manufacturer's model, which results in a direct comparison of first-line ipilimumab with DTIC or vemurafenib in terms of OS and PFS in previously untreated patients.

Superseded – see Erratum

The main concerns expressed by the ERG relate to the following issues:

1. *The treatment sequencing approach*

   Although conceptually it is valid to consider the sequencing of treatments and the ERG recognises that the approval of multiple treatments for advanced melanoma may lead to a sequential use of them in clinical practice. However, there are no reported results from any clinical trials comparing the sequential use and relative effect of treatments used in sequence for previously untreated advanced melanoma. This lack of evidence has led the manufacturer to oversimplify the treatment sequencing approach by using arbitrary assumptions about overall survival on second and third line treatments. In particular, the manufacturer's approach presents a switch in OS curves between first-, second-, and third-line (BSC) treatments, which is inconsistent and does not appear to have a clinical rationale underpinning the choice of curves in each line.

Furthermore, the ERG has some concerns about the choice of treatment permutations allowed in the model. There may be no concrete clinical guidelines to determine the exact sequence of treatments among the currently available therapies (DTIC, ipilimumab, vemurafenib and BSC) and the treatment patterns may still largely be subject to the individual clinicians' discretion. However, the manufacturer appears to have presented a partial and incomplete approach to modelling treatment sequences as there are a number of additional treatment permutations that could potentially be applied in clinical practice which the manufacturer has not considered in their analysis.

2. Modelling of OS and PFS

In the absence of data necessary to model the sequential use of treatments, the manufacturer has modelled second-line OS and PFS by adjusting the corresponding first-line curves downwards by an arbitrary hazard ratio based on data from the previous ipilimumab submission (TA268).[1] The ERG has concerns about the overall approach used for the downward adjustment and to the fact that the same adjustment was applied to vemurafenib despite been based on ipilimumab data. The ERG would have preferred to see the direct use of the OS and PFS curves for second-line treatment with ipilimumab applied in the sequential treatment model as this information was available from TA268,[1] which would have represented a more consistent use of survival data.

3. Modelling approach for Vemurafenib

For vemurafenib, OS and PFS data were informed from the BRIM-3 trial,[7] which did not have a comparative arm of ipilumumab. As a consequence, separate, independent arms of two different clinical trials were used to inform the relative efficacy of ipilimumab with vemurafenib in patients testing positive for the BRAF V600 mutation.

4. Costs of ipilimumab second line

The ERG noted that the first-line drug costs of ipilimumab per cycle (weekly cycles) were significantly different from the drug costs of ipilimumab per cycle when received second-line. There is a 42% difference in the drug cost of ipilimumab per cycle between second-line and first-line treatment ([redacted] vs. [redacted]). This difference is not discussed within the MS. The ERG recognises that the total costs first- and second-line will differ depending on the different proportions of patients receiving treatment but the ERG does not believe that there is any clinical reason why the acquisition cost of the drug per cycle in the model should differ between first- and second-line treatments. This represents an inconsistency in the model and is likely to be a key driver of the cost-effectiveness results.

5. *Health-related quality of life*

In the absence of EQ-5D data, the manufacturer used HRQoL data that were collected in the CA184-024 trial using the EORTC QLQ-C30 questionnaire,[5,30] which was used to derive utility values to inform the cost-effectiveness model by using the valuation algorithm by Rowen et al.[31] The ERG's main concern relates to the non-completion rates of the EORTC QLQ-C30 questionnaires. There were progressively lower completion rates at subsequent points in time, which may be associated with selection bias and may not capture the true HRQoL of patients receiving ipilimumab or DTIC. Furthermore, it was assumed that vemurafenib patients have the same HRQoL as ipilimumab patients. The manufacturer's use of time-dependent utility values based on proximity to death does not allow the positive response of treatment to be captured in the analysis.

Given the importance of a number of these issues, additional analyses undertaken by the ERG are presented in Section 6, which consider the potential impact of the remaining uncertainties on the cost-effectiveness results.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the manufacturer's cost-effectiveness analysis presented in Section 5, and challenges the manufacturer's estimate of cost-effectiveness on some of the clinical assumptions incorporated in the analysis.

The additional work undertaken by the ERG has three main elements:

1. Exploratory work by the ERG to identify the main drivers of cost-effectiveness and key assumptions for the different comparisons;
2. More detailed work exploring the robustness of the cost-effectiveness to specific assumptions and additional uncertainties identified by the ERG;
3. Presentation of the ERG's preferred base-case analysis.

The ERG's exploratory analysis focuses on the following seven issues and uncertainties:

1. Modelling the sequential use of treatment;
2. Use of a three-state model for first-line therapy;
3. Comparison of overall survival with ipilimumab 3mg/kg and ipilimumab 10mg/kg;
4. Concomitant DTIC in the CA184-024 study;
5. Relative efficacy of ipilimumab and vemurafenib based on an indirect comparison analysis;
6. Costs of ipilimumab second-line;
7. Health-related quality of life.

After demonstrating the uncertainty that surrounds the manufacturer's base-case results and the impact of the various assumptions on the ICER, the ERG presents its preferred base-case analysis.

6.2 Exploratory work by the ERG to identify the main drivers of cost-effectiveness and key assumptions for the different comparisons

Although the manufacturer undertook a detailed series of univariate sensitivity analyses, the ERG considered that it was difficult to establish the main drivers of the cost-effectiveness results and the impact of particular assumptions based on the evidence submitted by the manufacturer. Additional exploratory work was, therefore, undertaken by the ERG to clarify further the main drivers of cost-effectiveness and to identify the key assumptions within the submission. These key assumptions were then subjected to additional scrutiny and further re-analysis by the ERG.

The initial exploratory work by the ERG examined the OS and PFS curves for each of the sequential lines of treatment in order to examine the impact of the main treatment benefits assumed in the submission on the overall estimates of cost-effectiveness. This work was performed in a series of steps:

1. To begin, the ERG examined the BRAF V600 mutation-negative population for the comparison of ipilimumab with DTIC. This was the easier starting point since ipilimumab first-line is the only active treatment given before BSC. This was compared with first-line DTIC, which was following by ipilimumab second-line before BSC at third-line. A sensible starting point was to consider the number of life years on each line of therapy and its impact on cost-effectiveness.
2. The ERG then considered the assumptions made by the manufacturer about OS on second- and third-line therapy (BSC). The ERG examined a number of alternative assumptions for the OS curves on these latter lines of therapy. In this way, the ERG could examine how much of the cost-effectiveness was due to the assumptions and extrapolation of OS benefits.
3. Following this, the ERG extended the same exploration to the BRAF V600 mutation-positive population to see the impact of alternative assumptions regarding OS in this population.
4. Finally, given the impact of these assumptions, the ERG then 'turned off' the sequential use of treatments and only considered the cost-effectiveness of first-line treatment followed by BSC. For this simpler model structure, alternative assumptions about OS on BSC were also considered by the ERG.

The results of the ERG's analyses are outlined below.

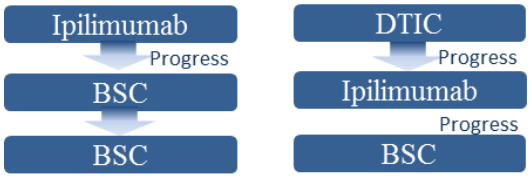
6.2.1 Modelling the sequential use of treatment

BRAF V600 mutation-negative population

As discussed in Section 5.2.4, the model structure developed by the manufacturer used a 'treatment sequencing' approach, where health states were defined based on the different lines of treatment that patients may follow. By adopting this approach, the manufacturer was forced to make a number of arbitrary assumptions about overall and progression-free survival on second- and third-line treatments, which were discussed in detail in Section 5.2.5. In this section, the ERG explores the impact of these assumptions on the estimate of cost-effectiveness. In particular, the ERG focuses on the implications of the switch between different survival curves on the latter lines of treatment (See Section 5.2.5.6).

For the BRAF V600 mutation-negative population, the only comparison with ipilimumab is that of DTIC. Figure 6.1 shows the treatment sequence modelled by the manufacturer for this sub-population.

Figure 6.1 Treatment sequence for ipilimumab first-line and DTIC first-line in BRAF V600 mutation-negative sub-population



In the base-case analysis, the manufacturer assumed that patients who receive ipilimumab first-line do not receive any other active therapies except those received as part of BSC (See Section 5.2.5.5 for the proportion of patients receiving different therapies as part of BSC). This is modelled by assuming that all patients follow the OS curve of first-line ipilimumab regardless of whether or not they progress to BSC. In contrast, patients who are treated with DTIC first-line follow the OS curve of DTIC up until the point of progression where they then switch to a better OS curve on second-line ipilimumab, but upon further progression, they then switch to BSC and move to the OS curve of first-line DTIC. In Section 5.2.5.6, the ERG argued that this switch between OS curves on second- and third-line treatments appeared to be arbitrary. The implications for the cost-effectiveness of ipilimumab compared with DTIC is to favour ipilimumab; the number of life years for first-line ipilimumab are 0.63 and 2.51 for ipilimumab and BSC, respectively, where all the life years incorporate the benefits of first-line ipilimumab without any additional costs associated with active therapies at second-line (only costs at second-line are those associated with BSC). In contrast for the comparator treatment of DTIC, the number of life years on each of the lines of treatment is 0.40 for first-line DTIC, 0.31 for second-line ipilimumab, and 1.22 for third-line BSC. Therefore, the comparator treatment receives the total costs of two-active drugs, DTIC and ipilimumab (as well as costs associated with BSC) but does not receive the full benefits of ipilimumab, which are only received for the duration of second-line treatment, where progression to BSC is modelled based on the OS of DTIC.

Scenarios 1, 2 and 3 below show the impact of the assumptions regarding OS on second- and third-line treatment on the estimate of cost-effectiveness. In scenario 1, for the comparator treatment of DTIC, overall survival for BSC is modelled by assuming that patients remain on the same OS curve of second-line treatment, which is consistent with the assumption used for ipilimumab, i.e. patients who survive and progress to BSC follow the downward adjusted OS curve of second-line ipilimumab instead of arbitrarily returning to the OS curve of first-line treatment. The impact on the cost-

effectiveness of ipilimumab is to increase the ICER from the manufacturer's base-case of £16,958 to £18,833.

In scenarios 2 and 3, the same overall survival curve is assumed for BSC for both ipilimumab and DTIC; in scenario 2, BSC is represented by the OS curve of ipilimumab second-line, while in scenario 3 BSC is represented by the OS curve of DTIC first-line. The resulting impact on the ICER is to increase it to £40,005 and £56,486 for scenarios 2 and 3, respectively. The ERG does not necessarily believe that scenario 3 is clinically plausible but it does highlight the impact of the manufacturer's assumptions regarding OS on BSC. For scenario 3, the sequence of treatments and assumptions used by the manufacturer remain the same for DTIC but for the comparator of ipilimumab, the survival benefits on BSC for ipilimumab are reduced to those which match BSC on DTIC.

The ERG considers scenario 1 to be the most clinically plausible and consistent scenario if the benefits of ipilimumab treatment are sustained over a long period. However, all 3 scenarios jointly demonstrate that the ICER is sensitive to the way that OS has been modelled in the manufacturer's submission.

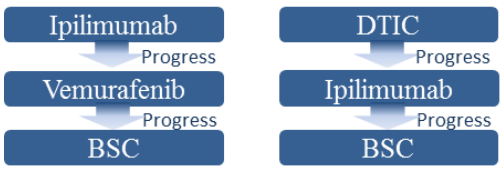
Table 6.1 Cost-effectiveness results for different assumptions on OS in second- and third-line for BRAF V600 mutation-negative subgroup; Ipilimumab vs DTIC

Scenario			Ipilimumab		DTIC		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Manufacturer's base-case									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£57,760	2.3527	£44,267	1.5570	£13,492	0.7956	£16,958
Scenario 1: OS for BSC, same as 2nd line									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS **Ipi 2nd line OS**	£57,760	2.3527	£44,910	1.6703	£12,850	0.6823	£18,833
Scenario 2: Same OS for BSC, Ipi 2nd line OS									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS **Ipi 2nd line OS** **Ipi 2nd line OS**	DTIC 1st line OS Ipi 2nd line OS **Ipi 2nd line OS**	£55,756	1.9415	£44,910	1.6703	£10,846	0.2711	£40,005
Scenario 3: Same OS for BSC, DTIC 1st line OS									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS **DTIC 1st line OS** **DTIC 1st line OS**	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£54,766	1.7429	£44,267	1.5570	£10,498	0.1859	£56,486

BRAF V600 mutation-positive population

The same exploration of OS on second- and third-line treatments was examined for the mutation-positive population. Figure 6.2 shows the treatment sequence modelled by the manufacturer for the comparison of ipilimumab with DTIC in the mutation-positive population.

Figure 6.2 Treatment sequence for ipilimumab first-line and DTIC first-line in BRAF V600 mutation-positive patients



The difference between this population and the mutation-negative is that vemurafenib was considered as a treatment option at second-line. In the base-case analysis, the manufacturer assumed that patients who receive ipilimumab treatment follow the OS curve of first-line treatment up until the point of progression. At the point of progression, patients then switch to second-line treatment on vemurafenib, where they follow the downward adjusted OS curve for second-line vemurafenib. When patients progress on second-line vemurafenib, they then switch to third-line BSC. At this point, patients who survive are assumed to follow the OS of first-line ipilimumab without any downward adjustment to the first-line OS curve. For the comparator of DTIC, the same approach as the mutation-negative population is used, where patients follow the OS of DTIC first-line up until the point of progression, then switch to OS on second-line ipilimumab before switching to BSC, which is then based on OS of first-line DTIC.

The impact of the modelling assumptions for OS is even more extreme in the BRAF V600 mutation-positive population. Scenario 4 (Table 6.2) shows the impact of assuming a consistent OS curve for BSC. This scenario is analogous to scenario 1 above, where OS for BSC is modelled by assuming that patients remain on the same OS curve of second-line treatment. The impact on the cost-effectiveness of ipilimumab is to increase the ICER markedly from the manufacturer's base-case of £31,559 to £941,091. The significant increase in the ICER is due to two factors: i) On ipilimumab, progression to third-line BSC no longer receives the long-tail of OS benefits from ipilimumab first-line but instead receives the OS benefits of second-line treatment of vemurafenib (which is modelled with a lower long-term survival than ipilimumab); and ii) the comparator of DTIC now benefits from the OS of second-line ipilimumab, whereas in the base-case it was assumed that the benefits were only received for the duration of second-line treatment (in contrast to the base-case analysis for ipilimumab where the benefits of ipilimumab were received much longer with BSC).

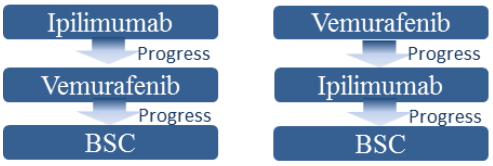
Scenarios 5 and 6 (Table 6.2) are analogous to scenarios 2 and 3 above, where the same overall survival curve is assumed for BSC for both ipilimumab and DTIC; in scenario 5, BSC is represented by the OS curve of ipilimumab second-line, while in scenario 6 BSC is represented by the OS curve of DTIC first-line. The resulting impact on the ICER is smaller, but still significant, by increasing the ICER from £31,559 to £71,335 and £81,893 for scenarios 5 and 6, respectively.

Table 6.2 Cost-effectiveness results for different assumptions on OS in second- and third-line for BRAF V600 mutation-positive subgroup; Ipilimumab vs DTIC

Scenario			Ipilimumab		DTIC		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Manufacturer's base-case									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£68,033	2.3101	£44,267	1.5570	£23,766	0.7531	£31,559
Scenario 4: OS for BSC, same as 2nd line									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS **Vem 2nd line OS**	DTIC 1st line OS Ipi 2nd line OS **Ipi 2nd line OS**	£65,301	1.6920	£44,910	1.6703	£20,391	0.0217	£941,091
Scenario 5: Same OS for BSC, Ipi 2nd line OS									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS **Ipi 2nd line OS**	DTIC 1st line OS Ipi 2nd line OS **Ipi 2nd line OS**	£66,431	1.9720	£44,910	1.6703	£21,521	0.3017	£71,335
Scenario 6: Same OS for BSC, DTIC 1st line OS									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS **DTIC 1st line OS**	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£65,630	1.8179	£44,267	1.5570	£21,363	0.2609	£81,893

A similar exploration of OS was examined for the comparison of ipilimumab with vemurafenib. Figure 6.3 shows the sequence of treatments modelled for this comparison.

Figure 6.3 Treatment sequence for ipilimumab first-line and vemurafenib first-line in BRAF V600 mutation-positive patients



The sequence for ipilimumab is the same as Figure 6.2 and the same assumptions were used by the manufacturer to model ipilimumab. For the comparison with vemurafenib, the manufacturer assumed that patients who receive vemurafenib follow the OS curve for first-line vemurafenib up until the point of progression. At the point of progression, patients are switched to second-line treatment on ipilimumab and follow the downward adjusted OS curve of second-line ipilimumab. When patients

progress to third-line BSC, it was assumed that they follow the OS curve of first-line vemurafenib. Again, the ERG notes the unfounded assumption that OS on BSC arbitrarily equates to that of first line treatment despite a switch to a different active treatment before progression to BSC. The implications on the cost-effectiveness results are shown in Table 6.3 for scenarios 7-10.

In the same manner as above, scenario 7 assumes that the OS curve for BSC in the comparison of ipilimumab with vemurafenib is the same as the corresponding second-line treatment (i.e. vemurafenib second-line OS is used to model survival on BSC for ipilimumab, while ipilimumab second-line OS is used to model survival on BSC for vemurafenib). The resulting impact on the cost-effectiveness estimate of ipilimumab is to remove it from the dominated region of the cost-effectiveness plane, where in the manufacturer's base-case analysis ipilimumab dominates vemurafenib, to the south-west quadrant where the ICER is £32,810 for vemurafenib compared with ipilimumab.

Similarly, scenarios 8 and 9, which assume the same overall survival curve for BSC for both ipilimumab and vemurafenib (scenario 8, BSC is represented by the OS curve of ipilimumab second-line and scenario 9, BSC is represented by the OS curve of vemurafenib second-line), results in a move from the dominated region of the cost-effectiveness plane to the south-west quadrant where the ICER is £73,666 and £84,980 for vemurafenib compared with ipilimumab for scenarios 8 and 9, respectively.

The ERG also explored an additional scenario for the comparison of ipilimumab with vemurafenib (scenario 10 in Table 6.3). This scenario examined the impact of the downward adjustment to the overall survival curves for second-line treatment. In Section 5.2.5.3, the ERG commented that the approach used by the manufacturer to estimate OS on second-line treatments was quite arbitrary by adjusting the first-line OS curves by a hazard ratio of 1.21. This hazard ratio, which was based on a comparison of the expected life years achieved by patients on second-line ipilimumab from TA268 with those on first-line ipilimumab, was also applied to the first-line OS curve of vemurafenib in order to generate the OS for second-line vemurafenib. In scenario 10, the implications of this adjustment are explored by examining the cost-effectiveness of ipilimumab without any adjustment to the first-line curves. The resulting ICER lies in the south-west quadrant of the cost-effectiveness plane, where the ICER is £27,180 for vemurafenib compared with ipilimumab.

Table 6.3 Cost-effectiveness results for different assumptions on OS in second- and third-line for BRAF V600 mutation-positive subgroup; Ipilimumab vs vemurafenib

Scenario			**Ipilimumab**		**Vemurafenib**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Manufacturer's base-case									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£68,033	2.3101	£80,658	2.1298	-£12,625	0.1803	Ipi dominates vem
Scenario 7: OS for BSC, same as 2nd line									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS **Vem 2nd line OS**	Vem 1st line OS Ipi 2nd line OS **Ipi 2nd line OS**	£65,301	1.6920	£80,959	2.1692	-£15,658	-0.4772	Ipi in SW Quadrant £32,810
Scenario 8: Same OS for BSC, Ipi 2nd line OS									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS **Ipi 2nd line OS**	Vem 1st line OS Ipi 2nd line OS **Ipi 2nd line OS**	£66,431	1.9720	£80,959	2.1692	-£14,528	-0.1972	Ipi in SW Quadrant £73,666
Scenario 9: Same OS for BSC, Vem 2nd line OS									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS **Vem 2nd line OS**	Vem 1st line OS Ipi 2nd line OS **Vem 2nd line OS**	£65,301	1.6920	£79,112	1.8545	-£13,812	-0.1625	Ipi in SW Quadrant £84,980
Scenario 10: Sequence of treatment, ipi followed by vem, vem followed by ipi									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS **Vem 1st line OS** **Vem 1st line OS**	Vem 1st line OS **Ipi 1st line OS** **Ipi 1st line OS**	£67,243	2.0384	£84,720	2.6814	-£17,478	-0.6430	Ipi in SW Quadrant £27,180

6.2.2 Use of a three-state model for first-line therapy

Given the implications of the assumptions used by the manufacturer to model the sequencing of treatments, which clearly substantially favours ipilimumab, the ERG 'turned off' the sequential use of treatments and only considered the cost-effectiveness of first-line treatment. The resulting model structure follows a conventional three-state cancer model with the only additional line of therapy being that of BSC. For this simpler model structure, alternative assumptions about OS on BSC were also explored.

The manufacturer presented the results of a three-state model in their sensitivity analysis (MS, p 200). For the comparison of ipilimumab with DTIC in both the BRAF V600 mutation-negative or –positive population, the corresponding ICER was £42,449 (Table 6.4). The results, however, assume that once patients progress to BSC, different OS curves are followed depending on treatment received at first-line, i.e. patients who receive ipilimumab continue to receive the survival benefits of ipilimumab despite progression to BSC, while patients who receive DTIC continue to receive the survival benefits of DTIC on progression to BSC. Scenario 11 (Table 6.4) explores the implications of this assumption by considering the same OS curves for patients who progress to BSC on ipilimumab and DTIC. In other words, the benefits of improved OS for ipilimumab are only achieved by patients who are progression-free; once patients progress, they have the same OS at DTIC. The resulting impact on the ICER is to increase it from £42,449 to £123,676.

The ERG recognises that it is unlikely that patients would suddenly switch to a lower survival curve at the point of progression. It is more likely that this switch would occur over time. Scenarios 12 and 13 attempt to model the switch in OS over time for patients who progress to BSC by considering how the first-line OS curve might converge to a lower survival curve at a later point in time. Without clinical evidence on which to base these scenarios, they represent only an exploration of the more plausible ICER, which is likely to lie somewhere between the two extremes of the manufacturer's ICER of £42,449 and the ICER of £123,676 from scenario 11. Once patients progress, scenario 12 assumes that OS on ipilimumab gradually converges to OS on DTIC between years 3 and 6 (Figure 6.4), while scenario 13 assumes that OS on ipilimumab gradually converges to DTIC between years 5 and 10 (Figure 6.5). The resulting impact on the ICER is to increase it from £42,449 to £86,825 and £64,184 for scenarios 12 and 13, respectively.

Table 6.4 Cost-effectiveness results for different assumptions on OS in BSC in the three-state model; Ipilimumab versus DTIC

Scenario			**Ipilimumab**		**DTIC**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Manufacturer's sensitivity analysis, three-state model									
	Ipilimumab	DTIC							
1st line BSC	Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS DTIC 1st line OS	£57,760	2.3527	£19,914	1.4611	£37,846	0.8916	£42,449
Scenario 11: Same OS curves for BSC									
	Ipilimumab	DTIC							
1st line BSC	Ipi 1st line OS **DTIC 1st line OS**	DTIC 1st line OS DTIC 1st line OS	£54,766	1.7429	£19,914	1.4611	£34,852	0.2818	£123,676
Scenario 12: OS for BSC, ipilimumab 1st line OS converges to DTIC 1st line OS between years 3 and 6									
	Ipilimumab	DTIC							
1st line BSC	Ipi 1st line OS **Ipi to DTIC OS**	DTIC 1st line OS DTIC 1st line OS	£55,697	1.8732	£19,914	1.4611	£35,783	0.4121	£86,825
Scenario 13: OS for BSC, ipilimumab 1st line OS converges to DTIC 1st line OS between years 5 and 10									
	Ipilimumab	DTIC							
1st line BSC	Ipi 1st line OS **Ipi to DTIC OS**	DTIC 1st line OS DTIC 1st line OS	£56,367	2.0290	£19,914	1.4611	£36,453	0.5679	£64,184

Figure 6.4 Ipilimumab first-line OS converges to DTIC first-line OS between years 3 and 6

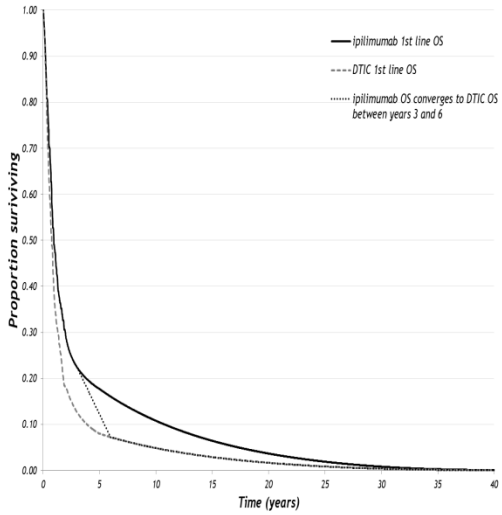
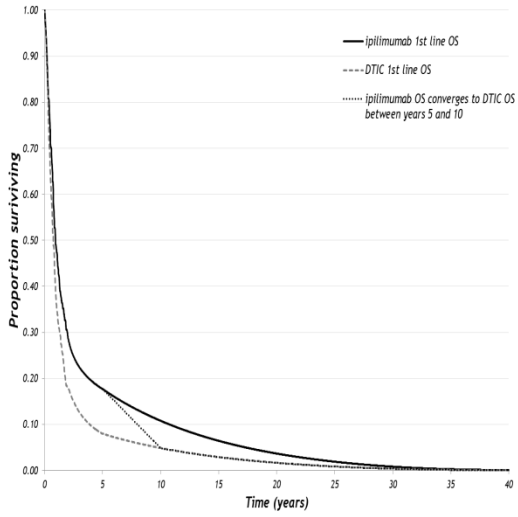


Figure 6.5 Ipilimumab first-line OS converges to DTIC first-line OS between years 5 and 10



A similar analysis was also undertaken for the comparison of ipilimumab with vemurafenib in the BRAF V600 mutation-positive population. Without modelling the sequencing of treatments, the manufacturer's sensitivity analysis for this comparison resulted in an ICER for ipilimumab of £28,980 (Table 6.5). Scenario 14 (Table 6.5) shows the implications on the cost-effectiveness results of assuming that patients who progress to BSC from either ipilimumab or vemurafenib, follow the same OS curves. The resulting impact on the ICER is much less favourable for ipilimumab as vemurafenib now dominates ipilimumab. Scenarios 15 and 16 consider a more gradual switch from the first-line OS curve to a lower survival curve at a later point in time for patients who progress. These scenarios are analogous to scenarios 12 and 13 above, where it is assumed that OS on ipilimumab gradually converges to OS on vemurafenib between years 3 and 6 (Scenario 15, Figure 6.6) and between years 5 and 10 (Scenario 16, Figure 6.7). For scenario 15, vemurafenib dominates ipilimumab, while for scenario 16 the ICER for ipilimumab is £83,861.

Table 6.5 Cost-effectiveness results for different assumptions on OS for BSC in the three-state model; Ipilimumab versus vemurafenib

Scenario			Ipilimumab		Vemurafenib		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Manufacturer's sensitivity analysis, three-state model									
	Ipilimumab	Vemurafenib							
1st line BSC	Ipi 1st line OS Ipi 1st line OS	Vem 1st line OS Vem 1st line OS	£57,760	2.3527	£52,346	2.1658	£5,414	0.1868	£28,980
Scenario 14: Same OS curves for BSC									
	Ipilimumab	Vemurafenib							
1st line BSC	Ipi 1st line OS **Vem 1st line OS**	Vem 1st line OS Vem 1st line OS	£57,097	2.0422	£52,346	2.1658	£4,751	-0.1236	Vem dominates ipi
Scenario 15: OS for BSC, ipilimumab 1st line OS converges to vem 1st line OS between years 3 and 6									
	Ipilimumab	Vemurafenib							
1st line BSC	Ipi 1st line OS **Ipi to vem OS**	Vem 1st line OS Vem 1st line OS	£56,927	2.1589	£52,346	2.1658	£4,581	-0.0069	Vem dominates ipi
Scenario 16: OS for BSC, ipilimumab 1st line OS converges to vem 1st line OS between years 5 and 10									
	Ipilimumab	Vemurafenib							
1st line BSC	Ipi 1st line OS **Ipi to vem OS**	Vem 1st line OS Vem 1st line OS	£57,205	2.2238	£52,346	2.1658	£4,859	0.0579	£83,861

Figure 6.6 Ipilimumab first-line OS converges to vemurafenib first-line OS between years 3 and 6

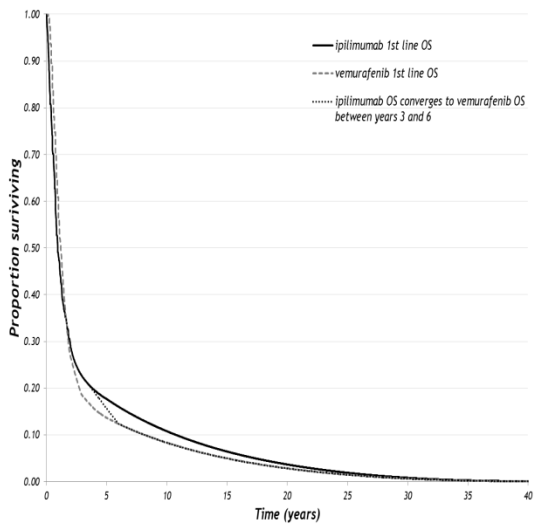
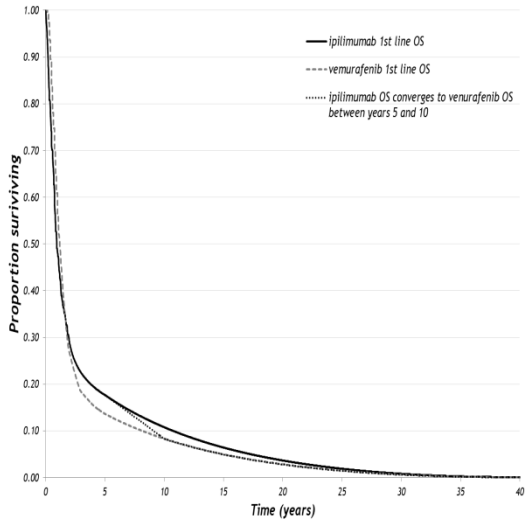


Figure 6.7 Ipilimumab first-line OS converges to vemurafenib first-line OS between years 5 and 10



6.2.3 Summary of the main drivers of cost-effectiveness

Based on the evidence submitted by the manufacturer, it is clear that the assumptions surrounding the sequencing of treatments have a major impact on the cost-effectiveness results. The ERG considers the approach used by the manufacturer to estimate OS on second-line treatments and third-line BSC as arbitrary. Furthermore, the switching of OS curves between lines of treatment is not only inconsistent but it is not clinically plausible and substantially favours the cost-effectiveness of ipilimumab. The main driver of cost-effectiveness lies in the assumptions used for OS on the latter lines of treatment. The cost-effectiveness of ipilimumab is achieved by assuming that patients who progress to BSC achieve the long-term benefits of sustained overall survival from ipilimumab first-line. The comparator treatment is disadvantaged by only receiving ipilimumab treatment second-line. The major flaw in the manufacturer's argument lies in the fact that patients who receive ipilimumab second-line cannot continue to receive the long-term benefits of sustained overall survival from ipilimumab second-line when they progress to BSC.

In light of these implausible assumptions by the manufacturer, the ERG believes that the only reasonable model structure on which to base the estimates of cost-effectiveness of ipilimumab is to consider first-line treatments only, which is consistent with the approach used in the previous appraisal of ipilimumab (TA268). However, the estimates of cost-effectiveness remain highly sensitive to the assumptions used to model progression on BSC.

6.3 Exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG

During the critique of the MS in Section 5.2.5, the ERG identified a number of uncertainties in relation to the comparative effectiveness estimates applied in the model. In particular, the ERG noted that the evidence for the cost-effectiveness of ipilimumub within it licensed dose of 3mg/kg every 3 weeks for a total of 4 doses was based on the efficacy of ipilimumab 10mg/kg in addition to DTIC therapy from the CA184-024 trial,[5] and the use of separate, independent arms from different clinical trials (i.e. breaking randomisation) was used to establish the relative efficacy with vemurafenib. Furthermore, the method used for the comparison with vemurafenib was inconsistent with the values reported from the indirect comparison analysis, which was also undertaken by the manufacturer. Given the importance of the clinical evidence as a driver of cost-effectiveness, the ERG has examined a set of individual comparisons for both the BRAF V600 mutation-negative and –positive populations where the assumptions on the clinical evidence have been varied. The ERG also noted in Section 5.2.7.3 that the costs of ipilimumab per weekly cycle were considerably higher with ipilimumab treatment second-line compared with ipilimumab first-line. The implications of this cost difference on the cost-effectiveness results are explored below. The ERG has also explored in a scenario analysis the implications of using time-to-death HRQoL outcomes by alternatively assigning utility values to pre- and post-progression health states.

Superseded – see Erratum

6.3.1 Comparison of overall survival with ipilimumab 3mg/kg and ipilimumab 10mg/kg

In the absence of sufficient evidence for previously untreated patients, the manufacturer assumed equivalent efficacy between 3mg/kg dose of ipilimumab and 10mg/kg dose in terms of both overall and progression-free survival. However, as discussed in Sections 4.2.3.1 and 4.5, from the CA184-022 trial of previously treated and untreated patients, median overall survival appeared to be better in the 10 mg/kg treatment group but the difference was not statistically significant.[12] A very small trial of previously treated and untreated patients (CA184-004) found no meaningful differences in clinical activity between the two ipilimumab doses.[13] The ERG requested further clarification on this point and asked the manufacturer to provide a comparison of ipilimumab 3mg/kg and ipilimumab 10mg/kg in both the treatment-naïve subgroup population and the whole population (both previously treated and untreated) in all clinical trials.[14] In response the manufacturer presented results from a pooled data analysis comparing OS profiles of ipilimumab 3mg/kg (MDX010-20; CA184-022) and 10mg/kg (CA184-007; CA184-008; CA184-022) for a mixed (both previously treated and untreated) patient population. The Kaplan-Meier curves for this pooled data analysis are presented in Figure 4.6, Section 4.2.3.2 (a digitisation of the curves is also presented below in Figure 6.8). The manufacturer reported that no significant difference in survival was observed between the ipilimumab 3mg/kg and 10mg/kg treatment arms in the whole population analyses. However, the ERG notes that the

difference is more prominent at different time points. Over the 70 month time period, the pooled analysis suggests that a 10 mg/kg dose is better than a 3 mg/kg dose in terms of overall survival. Furthermore, the 95% confidence intervals barely cross between 15 and 70 months suggesting a statistically significant difference. Therefore, in the ERG's view, there is currently no conclusive evidence that ipilimumab at a dose of 3 mg/kg is as clinically effective as a dose of 10 mg/kg. The implications of this assumption on the estimate of cost-effectiveness are explored below.

In order to estimate the implied hazard ratio for 3mg/kg relative to 10mg/kg, the ERG digitised the Kaplan-Meier curves for ipilimumab 3mg/kg and ipilimumab 10mg/kg over the period of 70 months, as shown in Figure 6.8. The resulting implied hazard ratio was [redacted] for ipilimumab 3mg/kg. Although the ERG recognises that the assumption of proportional hazards is unlikely to hold over all time periods, the implied hazard ratio does provide an estimate of the relative effectiveness of 3mg/kg compared with 10mg/kg. The ERG applied this hazard ratio to the ipilimumab 10mg/kg OS curve from the CA184-024 trial[5] (which is used in the manufacturer's base-case analysis) to estimate the 3mg/kg OS curve for ipilimumab. Figure 6.8 shows that the estimated OS curve for 3mg/kg based on the implied hazard ratio is not very far off the actual 3mg/kg curve across all time points.

Scenarios 17, 18, and 19 (Tables 6.6 – 6.8) show the estimated cost-effectiveness results for the licenced dose of ipilimumab 3mg/kg based on the adjusted overall survival of ipilimumab 10mg/kg. Since the overall survival benefits of ipilimumab are less for 3mg/kg, the ICER for ipilimumab compared with DTIC increases from the base-case value of £16,958 to £59,942 in the BRAF V600 mutation-negative population, and from £31,559 to £85,806 in the mutation-positive population. For the comparison with vemurafenib, ipilimumab no longer appears less costly and more effective as in the manufacturer's base-case analysis, but instead moves to the south-west quadrant of the cost-effectiveness plane (i.e. ipilimumab is less effective and less costly than vemurafenib) with a resulting ICER of £56,958 for vemurafenib compared with ipilimumab.

BRAF V600 mutation-negative population, comparison of ipilimumab with DTIC

Table 6.6 Cost-effectiveness results when OS is adjusted to 3mg/kg dosing regimen; Ipilimumab versus DTIC

Scenario			**Ipilimumab**		**DTIC**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Manufacturer's base-case: Based on ipilimumab 10mg/kg									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£57,760	2.3527	£44,267	1.5570	£13,492	0.7956	£16,958
Scenario 17: Ipilimumab OS adjusted to 3mg/kg									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£52,869	1.5606	£41,600	1.3726	£11,270	0.1880	£59,942

BRAF V600 mutation-positive population, comparison of ipilimumab with DTIC

Table 6.7 Cost-effectiveness results when OS is adjusted to 3mg/kg dosing regimen; Ipilimumab versus DTIC

Scenario			**Ipilimumab**		**DTIC**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Manufacturer's base-case: Based on ipilimumab 10mg/kg									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£68,033	2.3101	£44,267	1.5570	£23,766	0.7531	£31,559
Scenario 18: Ipilimumab OS adjusted to 3mg/kg									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£62,228	1.6130	£41,600	1.3726	£20,629	0.2404	£85,806

BRAF V600 mutation-positive population, comparison of ipilimumab with vemurafenib

Table 6.8 Cost-effectiveness results when OS is adjusted to 3mg/kg dosing regimen; Ipilimumab versus vemurafenib

Scenario			**Ipilimumab**		**Vemurafenib**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Manufacturer's base-case – Based on ipilimumab 10mg/kg									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£68,033	2.3101	£80,658	2.1298	-£12,625	0.1803	Ipi dominates vem
Scenario 19: Ipilimumab OS adjusted to 3mg/kg									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£62,228	1.6130	£76,956	1.8716	-£14,728	-0.2586	Ipi in SW Quadrant £56,958

Figure 6.8 [redacted]

[redacted]

6.3.2 Concomitant DTIC

The manufacturer's assessment of cost-effectiveness is based on comparative effectiveness evidence on the efficacy of ipilimumab 10mg/kg in addition to DTIC therapy from the CA184-024 trial.[5] In Sections 4.2.3.1 and 4.5, the ERG makes the case that there is no conclusive evidence that ipilimumab monotherapy is as clinically effective as ipilimumab plus DTIC. In Table 16, page 69 of the MS, the manufacturer presents the results of the MDX010-08 trial, which showed that the hazard ratio for

ipilimumab 3mg/kg + DTIC compared with ipilimumab 3mg/kg monotherapy is 0.75. The ERG used this hazard ratio to explore the cost-effectiveness of ipilimumab monotherapy. In a similar manner to the analysis presented above, the ERG adjusted the OS curve for first-line ipilimumab from the CA184-024 trial (ipilimumab10mg/kg + DTIC) in order to examine the effects of concomitant DTIC on the estimates of cost-effectiveness.[5]

Scenarios 20, 21, and 22 (Tables 6.9 - 6.11) show the estimated cost-effectiveness results for ipilimumab monotherapy based on the adjusted overall survival of ipilimumab 10mg/kg in addition to DTIC therapy. Since the overall survival benefits of ipilimumab monotherapy are less than ipilimumab with concomitant DTIC based on the MDX010-08 trial, the ICER for ipilimumab compared with DTIC increases from the base-case value of £16,958 to £73,615 in the BRAF V600 mutation-negative population, and from £31,559 to £97,864 in the mutation-positive population. For the comparison with vemurafenib, ipilimumab no longer appears less costly and more effective as in the manufacturer's base-case analysis, but instead moves to the south-west quadrant of the cost-effectiveness plane with a resulting ICER of £52,199 for vemurafenib.

These scenarios in conjunction with scenarios 17-19 suggest that the manufacturer's assumption of equivalent efficacy between ipilimumab 3mg/kg monotherapy and ipilimumab 10mg/kg in addition to DTIC therapy may substantially favour the cost-effectiveness of ipilimumab.

BRAF V600 mutation-negative population, comparison of ipilimumab with DTIC

Table 6.9 Cost-effectiveness results for ipilimumab monotherapy based on the adjusted overall survival of ipilimumab 10mg/kg in addition to DTIC therapy; Ipilimumab versus DTIC

Scenario			**Ipilimumab**		**DTIC**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Manufacturer's base-case: Based on ipilimumab 10mg/kg + DTIC trial evidence									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£57,760	2.3527	£44,267	1.5570	£13,492	0.7956	£16,958
Scenario 20: Ipilimumab OS adjusted for concomitant DTIC									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£52,520	1.5095	£41,331	1.3575	£11,189	0.1520	£73,615

BRAF V600 mutation-positive population, comparison of ipilimumab with DTIC

Table 6.10 Cost-effectiveness results for ipilimumab monotherapy based on the adjusted overall survival of ipilimumab 10mg/kg in addition to DTIC therapy; Ipilimumab versus DTIC

Scenario			**Ipilimumab**		**DTIC**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Manufacturer's base-case: Based on ipilimumab 10mg/kg + DTIC trial evidence									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£68,033	2.3101	£44,267	1.5570	£23,766	0.7531	£31,559
Scenario 21: Ipilimumab OS adjusted for concomitant DTIC									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£61,794	1.5666	£41,331	1.3575	£20,463	0.2091	£97,864

BRAF V600 mutation-positive population, comparison of ipilimumab with vemurafenib

Table 6.11 Cost-effectiveness results for ipilimumab monotherapy based on the adjusted overall survival of ipilimumab 10mg/kg in addition to DTIC therapy; Ipilimumab versus vemurafenib

Scenario			**Ipilimumab**		**Vemurafenib**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Manufacturer's base-case: Based on ipilimumab 10mg/kg + DTIC trial evidence									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£68,033	2.3101	£80,658	2.1298	-£12,625	0.1803	Ipi dominates vem
Scenario 22: Ipilimumab OS adjusted for concomitant DTIC									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£61,794	1.5666	£76,605	1.8503	-£14,811	-0.2837	Ipi in SW Quadrant £52,199

6.3.3 Relative efficacy of ipilimumab and vemurafenib based on an indirect comparison analysis

As discussed in Section 5.2.5.1, the manufacturer used separate, independent arms from different clinical trials (i.e. breaking randomisation) to establish the relative efficacy of ipilimumab with vemurafenib. This method resulted in inconsistent estimates of relative efficacy with those reported in the MS from an indirect treatment comparison analysis (MS, p 79), which was not subsequently used in the model. The indirect comparison of ipilimumab in addition to DTIC with vemurafenib for overall survival resulted in a HR of 1.16 for ipilimumab + DTIC. The ERG requested clarification from the manufacturer on the reasons for presenting the indirect comparison analysis but not subsequently using the results in the modelling. In response the manufacturer stated that the analysis was not used because inspection of the Nelson-Aalen plots revealed that the hazards were not constant over time; therefore, a single hazard ratio could not be applied accurately to the entire life expectancy of patients. Instead, the manufacturer performed a direct comparison of two independent arms from separate trials, which implies a strong assumption about the exchangeability of the two trial populations (CA184-024[5] and BRIM-3). The implied hazard ratios for the comparison of ipilimumab with vemurafenib in the modelled extrapolation were 1.256 at year 1, 0.938 between years 1 and 2, 0.883 between years 2 and 3, 0.877 between years 3 and 4, and 0.874 between years 4 and 5.

Although the ERG recognises that the assumption of proportional hazards may not hold over the entire time period, the manufacturer's assumption regarding exchangeability of trial populations is also a strong assumption. Therefore, the ERG considers an alternative scenario based on the results of the indirect comparison analysis. The ERG applied the hazard ratio from the indirect comparison to the overall survival of first-line ipilimumab in order to estimate OS on vemurafenib. Scenario 23 shows the impact on the estimate of cost-effectiveness of ipilimumab compared with vemurafenib in the BRAF V600 mutation-positive population. While ipilimumab appeared to dominate vemurafenib in the manufacturer's base-case analysis, the results of the indirect comparison shows that ipilimumab is less costly but also less effective compared with vemurafenib. In this case, the ICER of £45,410 for vemurafenib versus ipilimumab is in the south-west quadrant of the cost-effectiveness plane.

BRAF V600 mutation-positive population, comparison of ipilimumab with vemurafenib

Table 6.12 Cost-effectiveness results when the indirect analysis outcomes are adopted

Scenario			**Ipilimumab**		**Vemurafenib**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Manufacturer's base-case: Independent arms from separate trials									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£68,033	2.3101	£80,658	2.1298	-£12,625	0.1803	Ipi dominates vem
Scenario 23: Vem 1st line OS based on indirect comparison HR applied to ipi 1st line OS									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£67,902	2.3298	£77,322	2.5372	-£9,420	-0.2074	Ipi in SW Quadrant £45,410

6.3.4 Costs of ipilimumab second line

The ERG noted in Section 5.2.7.3 that the costs of ipilimumab per weekly cycle were considerably higher with ipilimumab treatment second-line ([redacted]) compared with ipilimumab treatment first-line ([redacted]). The discrepancy arose from the way that the manufacturer incorporated the costs of second-line treatments in the model. The costs of second-line ipilimumab were incorporated in the model as a cost per cycle based on average costs calculated from the previous submission of ipilimumab (TA268), whereas a cost per dose was applied in the model for first-line ipilimumab. This resulted in a disparity between the acquisition drug costs of ipilimumab first- and second-line, which is not discussed in the MS. The total costs of first- and second-line therapy will differ depending on the different proportions of patients surviving to receive treatment, but the ERG does not believe that there is any clinical reason why the acquisition cost of the drug per weekly cycle should differ between first- and second-line treatments.

In Scenarios 24, 25 and 26 (Tables 6.13-6.15), the ERG explores the implications of the cost difference on the estimates of cost-effectiveness by allocated equal acquisition costs per cycle ([redacted]) to ipilimumab first- and second-line. For the BRAF V600 mutation-negative population, this scenario increases the ICER from £16,958 in the manufacturer's base-case to £25,720. For the BRAF V600 mutation-positive population, the ICER for ipilimumab compared with DTIC increases from £31,559 to £40,816, while ipilimumab continues to dominate vemurafenib.

BRAF V600 mutation-negative population, comparison of ipilimumab with DTIC

Table 6.13 Cost-effectiveness results when same costs are assumed for ipilimumab first and second line; Ipilimumab versus DTIC

Scenario			Ipilimumab		DTIC		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Manufacturer's base-case – Higher costs per cycle for ipilimumab 2nd line compared with ipilimumab 1st line									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£57,760	2.3527	£44,267	1.5570	£13,492	0.7956	£16,958
Scenario 24: Same costs per cycle for ipilimumab 1st and 2nd line									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£57,760	2.3527	£37,296	1.5570	£20,463	0.7956	£25,720

BRAF V600 mutation-positive population, comparison of ipilimumab with DTIC

Table 6.14 Cost-effectiveness results when same costs are assumed for ipilimumab first and second line; Ipilimumab versus DTIC

Scenario			Ipilimumab		DTIC		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Manufacturer's base-case – Higher costs per cycle for ipilimumab 2nd line compared with ipilimumab 1st line									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£68,033	2.3101	£44,267	1.5570	£23,766	0.7531	£31,559
Scenario 25: Same costs per cycle for ipilimumab 1st and 2nd line									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£68,033	2.3101	£37,296	1.5570	£30,737	0.7531	£40,816

BRAF V600 mutation-positive population, comparison of ipilimumab with vemurafenib

Table 6.15 Cost-effectiveness results when same costs are assumed for ipilimumab first and second line; Ipilimumab versus vemurafenib

Scenario			Ipilimumab		Vemurafenib		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Manufacturer's base-case – Higher costs per cycle for ipilimumab 2nd line compared with ipilimumab 1st line									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£68,033	2.3101	£80,658	2.1298	-£12,625	0.1803	Ipi dominates vem
Scenario 26: Same costs per cycle for ipilimumab 1st and 2nd line									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£68,033	2.3101	£72,271	2.1298	-£4,237	0.1803	Ipi dominates vem

6.3.5 Health-related quality of life

The manufacturer quantified HRQoL outcomes in the model differently from conventional three-state cancer models by using time-to-death utility values instead of pre- and post-progression health state utility values. The ERG explored the impact of this alternative modelling approach by comparing the estimates of cost-effectiveness with those based on utility values for pre- and post-progression as used in the previous submission of ipilimumab for previously treated patients (TA268). The utility values for pre- and post-progression were 0.80 and 0.76, respectively, based on Batty 2011.[54]

Scenarios 27, 28, and 29 (Tables 6.16 - 6.18) show that the ICER is less sensitive to this assumption compared with many of the other scenarios presented above. The ICER increased from £16,958 to £19,320 for the comparison of ipilimumab with DTIC in the BRAF V600 mutation-negative population, while it increased from £31,559 to £35,717 in the mutation-positive population. For the comparison with vemurafenib, ipilimumab appeared to remain dominant over vemurafenib.

BRAF V600 mutation-negative population, comparison of ipilimumab with DTIC

Table 6.16 Cost-effectiveness results when pre- and post-progression utility values are assumed; Ipilimumab versus DTIC

Scenario			Ipilimumab		DTIC		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Manufacturer's base-case: Time to death utility values									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£57,760	2.3527	£44,267	1.5570	£13,492	0.7956	£16,958
Scenario 27: Pre- and post-progression utility values									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£57,760	2.1118	£44,267	1.4134	£13,492	0.6984	£19,320

BRAF V600 mutation-positive population, comparison of ipilimumab with DTIC

Table 6.17 Cost-effectiveness results when pre- and post-progression utility values are assumed; Ipilimumab versus DTIC

Scenario			Ipilimumab		DTIC		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Manufacturer's base-case: Time to death utility values									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£68,033	2.3101	£44,267	1.5570	£23,766	0.7531	£31,559
Scenario 28: Pre- and post-progression utility values									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS DTIC 1st line OS	£68,033	2.0788	£44,267	1.4134	£23,766	0.6654	£35,717

BRAF V600 mutation-positive population, comparison of ipilimumab with vemurafenib

Table 6.18 Cost-effectiveness results when pre- and post-progression utility values are assumed; Ipilimumab versus vemurafenib

Scenario			Ipilimumab		Vemurafenib		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Manufacturer's base-case: Time to death utility values									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£68,033	2.3101	£80,658	2.1298	-£12,625	0.1803	Ipi dominates vem
Scenario 29: Pre- and post-progression utility values									
	Ipilimumab	Vemurafenib							
1st line 2nd line BSC	Ipi 1st line OS Vem 2nd line OS Ipi 1st line OS	Vem 1st line OS Ipi 2nd line OS Vem 1st line OS	£68,033	2.0788	£80,658	1.9268	-£12,625	0.1520	Ipi dominates vem

6.4 ERG's preferred analysis (base-case)

Based on the additional exploratory work by the ERG to address several of the remaining issues and uncertainties identified during the structured critique of the manufacturer's cost-effectiveness analysis, the ERG presents its preferred base-case analysis below.

The ERG believes that the only reasonable model structure on which to base the estimates of cost-effectiveness of ipilimumab is to consider first-line treatments only, which essentially uses a conventional three-state model based on pre-progression, post-progression, and death, with BSC being the only second-line treatment considered. This approach is consistent with that used in the previous appraisal of ipilimumab (TA268). However, as shown in Section 6.2, the estimates of cost-effectiveness remain highly sensitive to the assumptions used to model overall survival on BSC.

The most important scenarios presented above relate to the uncertainties surrounding the comparative effectiveness estimates of ipilimumab with DTIC and vemurafenib. There is a lack of comparative evidence for ipilimumub within its licensed dose of 3mg/kg. The ERG has explored the cost-effectiveness of ipilimumab 3mg/kg monotherapy by adjusting the overall survival curve for ipilimumab 10mg/kg concomitant with DTIC. Taking the three-state model as the ERG's preferred base-case, the impact of this adjustment on the estimate of cost-effectiveness is presented in Table 6.19. For the comparison of ipilimumab with DTIC in the mutation-positive or -negative population, the adjustment for 3mg/kg yields considerably lower QALYs (2.35 QALYs compared with the base-case of 1.56 QALYs) and results in a multi-fold higher ICER of £331,091 (Scenario A). The

concomitant effect of DTIC has an even more remarkable effect on the ICER by increasing it to £674,144 (Scenario B). For the comparison of ipilimumab with vemurafenib, vemurafenib dominates ipilimumab in both scenarios A and B.

BRAF V600 mutation-negative or –positive population, comparison of ipilimumab with DTIC

Table 6.19 Cost-effectiveness of ipilimumab adjusted for 3mg/kg and concomitant DTIC, taking the three-state model as the ERG's preferred base-case; Ipilimumab versus DTIC

Scenario			**Ipilimumab**		**DTIC**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Three-state model									
	Ipilimumab	DTIC							
1st line BSC	Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS DTIC 1st line OS	£57,760	2.3527	£19,914	1.4611	£37,846	0.8916	£42,449
Scenario A: Ipilimumab OS adjusted to 3mg/kg									
	Ipilimumab	DTIC							
1st line BSC	Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS DTIC 1st line OS	£52,869	1.5606	£19,914	1.4611	£32,955	0.0995	£331,091
Scenario B: Ipilimumab OS adjusted for concomitant DTIC									
	Ipilimumab	DTIC							
1st line BSC	Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS DTIC 1st line OS	£52,520	1.5095	£19,914	1.4611	£32,606	0.0484	£674,144

BRAF V600 mutation-positive population, comparison of ipilimumab with vemurafenib

Table 6.20 Cost-effectiveness of ipilimumab adjusted for 3mg/kg and concomitant DTIC, taking the three-state model as the ERG's preferred base-case; Ipilimumab versus vemurafenib

Scenario			**Ipilimumab**		**Vemurafenib**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Three-state model									
	Ipilimumab	vemurafenib							
1st line BSC	Ipi 1st line OS Ipi 1st line OS	Vem 1st line OS Vem 1st line OS	£57,760	2.3527	£52,346	2.1658	£5,414	0.1868	£28,980
Scenario A: Ipilimumab OS adjusted to 3mg/kg									
	Ipilimumab	Vemurafenib							
1st line BSC	Ipi 1st line OS Ipi 1st line OS	Vem 1st line OS Vem 1st line OS	£52,869	1.5606	£52,346	2.1658	£524	-0.6052	Vem dominates ipi
Scenario B: Ipilimumab OS adjusted for concomitant DTIC									
	Ipilimumab	Vemurafenib							
1st line BSC	Ipi 1st line OS Ipi 1st line OS	Vem 1st line OS Vem 1st line OS	£52,520	1.5095	£52,346	2.1658	£174	-0.6564	Vem dominates ipi

7 End of life

The MS states that advanced melanoma patients have a short life expectancy with a median survival of 6-9 months. The ERG agrees that life expectancy of patients with advanced melanoma is likely to meet NICE's End of Life criteria. One year survival for patients diagnosed with stage IV disease is estimated to be around 10% for men and 35% for women, and five year survival is estimated to be around 8% for men and 25% for women.[19]

In the CA184-024 trial of ipilimumab 10 mg/kg plus DTIC versus DTIC alone, median overall survival was increased by 2.1 months (11.2 months versus 9.1 months; $p<0.001$),[5] which does not meet NICE's End of Life criteria of an extension to life of at least an additional three months. The MS states that restricted mean analysis (carried out on patient level data from the 5 year cut of CA184-024) shows a survival gain of 5.7 months over the 5 year trial (MS page 65); however, these data are not presented elsewhere in the MS, so cannot be verified. In addition, there is no direct evidence for the effectiveness of ipilimumab at its licensed dose of 3 mg/kg compared with current NHS treatment for previously untreated, advanced melanoma patients, and there is currently no conclusive evidence that ipilimumab at a dose of 3 mg/kg is as clinically effective as a dose of 10 mg/kg; therefore, based on the evidence presented, the survival benefit may be overestimated in the MS.

In Section C of the MS, the manufacturer estimated of the number of patients eligible for treatment with ipilimumab in England and Wales, by calculating the proportion of malignant melanoma patients with stage IIIc or IV disease from the overall incidence. The number of patients anticipated to be eligible for treatment in 2014 is estimated at 1319. Therefore, the number of patients indicated for ipilimumab treatment meets NICE's End of Life criteria.

8 Overall conclusions

Evidence from a good quality RCT demonstrates that ipilimumab 10 mg/kg plus DTIC (including a maintenance phase of ipilimumab therapy) significantly increases overall survival compared with DTIC alone (median overall survival increase of 2.1 months).[5] However, this trial does not provide direct evidence for the effectiveness of ipilimumab 3 mg/kg monotherapy (without maintenance therapy) compared with DTIC, vemurafenib or dabrafenib for the treatment of previously untreated, advanced melanoma patients.

The MS presents indirect comparisons of ipilimumab plus DTIC, vemurafenib and dabrafenib, however, the ERG does not consider these indirect comparisons to be appropriate because of the differences in trial populations between the three included trials.

There is currently no conclusive evidence that ipilimumab at a dose of 3 mg/kg is as clinically effective as a dose of 10 mg/kg. It was a condition of the EMA marketing authorisation that a trial was undertaken to directly compare the clinical effectiveness and safety of ipilimumab at the 3 mg/kg and 10 mg/kg doses; this trial is the ongoing CA184-169 trial.[17]

Based on the evidence presented, the ERG considers that the survival benefit may be overestimated in the MS.

However, whilst there is a lack of direct evidence of the clinical effectiveness of 3 mg/kg ipilimumab monotherapy for the treatment of previously untreated advanced melanoma patients, the available RCT evidence (both first-line and second-line) consistently demonstrates increased overall survival with ipilimumab compared with DTIC or gp100 vaccine.[5, 18]

The manufacturer's *de-novo* economic analysis was used to estimate the cost-effectiveness of ipilimumab in the BRAF V600 mutation-positive and –negative populations. The cost-effectiveness of first-line therapy (ipilimumab compared with DTIC or vemurafenib) was assessed by using a treatment sequencing approach which incorporated second-line active therapy (ipilimumab or vemurafenib) and third-line BSC. The results from the manufacturer's submission were presented as separate pair-wise comparisons of the ICER for ipilimumab with DTIC in the mutation-negative (£16,958 per QALY) and –positive populations (£31,559 per QALY) and ipilimumab with vemurafenib in the mutation-positive population (ipilimumab dominates vemurafenib with less costs and more QALYs). The results of the manufacturer's sensitivity analyses indicated that the ICER estimates were most sensitive to the assumptions used to model overall survival of ipilimumab and DTIC, time spent on second-line treatments, and time spent on first-line treatment with ipilimumab relative to DTIC.

The ERG considers the manufacturer's base-case ICERs to be highly uncertain and overly optimistic towards ipilimumab. A number of critical assumptions around the sequencing of treatments underpin the manufacturer's base-case results. The ERG highlighted that the cost-effectiveness of ipilimumab was achieved in the manufacturer's analysis by assuming that patients who progress to BSC following first-line ipilimumab achieve the long-term benefits of sustained overall survival from ipilimumab first-line. However, for the comparator treatment (DTIC or vemurafenib) patients who receive ipilimumab second-line cannot continue to receive the long-term benefits of sustained overall survival from ipilimumab second-line when they progress to BSC, instead they return to the lower overall survival of the first-line treatment (DTIC or vemurafenib). The manufacturer's analysis also included a number of highly uncertain assumptions about the relative efficacy of the treatments. The ERG believes that the only reasonable model structure on which to base the estimates of cost-effectiveness of ipilimumab is to consider first-line treatments only, which considers a conventional three-state model based on pre-progression, post-progression, and death, with BSC being the only second-line treatment considered. This approach would be consistent with that used in the previous appraisal of ipilimumab (TA268).

The ERG attempted to address some of the issues and uncertainties by conducting separate analyses using the manufacturer's model. The ERG's exploratory analyses focused on the implications for cost-effectiveness of modelling sequential use of treatments, overall survival on different doses of ipilimumab (3mg/kg versus 10mg/kg), effects of concomitant DTIC therapy with ipilimumab, relative efficacy estimates for ipilimumab and vemurafenib, costs associated with second-line treatment of ipilimumab, and assumptions regarding HRQoL utility values. The manufacturer's assumptions surrounding the sequencing of treatments had a major impact on the cost-effectiveness results. The manufacturer's base-case ICER for the comparison of ipilimumab with DTIC in the mutation-negative population increased from £16,958 per QALY to between £18,833 and £56,486 per QALY. For the same comparison in the mutation-positive population, the manufacturer's base-case ICER increased from £31,559 to between £71,335 and £941,091 per QALY. For the comparison with vemurafenib in the mutation-positive population, the ICER of ipilimumab which dominated vemurafenib in the manufacturer's base-case analysis moved to the south-west quadrant of the cost-effectiveness plane resulting in an ICER for vemurafenib of between £27,180 and £84,980. The assumptions surrounding the manufacturer's comparative effectiveness estimates of ipilimumab with DTIC and vemurafenib also had a major impact on the cost-effectiveness results. For the comparison of ipilimumab with DTIC in the mutation-positive or -negative population, the adjustment for 3mg/kg dose of ipilimumab resulted in an ICER of £331,091 per QALY using the three-state model, while the adjustment for concomitant DTIC resulted in an ICER of £674,144 per QALY for the same comparison.

8.1 Implications for research

Further research is required to establish more clearly the place of ipilimumab within the treatment pathway of patients with malignant melanoma. Ipilimumab provides a survival benefit to some patients, but as yet it is not possible to predict who these patients will be prior to treatment.

There are many ongoing trials of ipilimumab for patients with advanced melanoma, including several trials of ipilimumab in combination with other treatments, e.g. kinase inhibitors such as vemurafenib, trametinib and dabrafenib and immunotherapies, such as interferon alfa-2b, nivolumab and talimogene laherparepvec.

Of particular relevance is the ongoing RCT comparing two different doses of ipilimumab; 3 mg/kg versus 10 mg/kg (CA184-169),[17] which was a condition of the marketing authorisation of ipilimumab by the EMA.[16]

A randomised phase III trial of ipilimumab followed by vemurafenib versus vemurafenib followed by ipilimumab is planned (ECOG E1612) in BRAF V600 positive patients,[21] which will inform the sequencing of treatment for these patients.

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