NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Ipilimumab for previously untreated unresectable malignant melanoma

This premeeting briefing is a summary of:

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

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

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The manufacturer's submission is based on the assumption that 3 mg/kg and 10 mg/kg doses of ipilimumab are clinically equivalent and that ipilimumab alone has the same effectiveness as ipilimumab plus dacarbazine. Does the Committee agree with these assumptions given the European Medicines Agency's (EMA) consideration outlined in 4.11 and the concerns outlined by the ERG around these assumptions?
- The manufacturer included dabrafenib as a comparator for BRAF V600 mutation-positive patients in the clinical section, however it was not part of the NICE scope and no data was available to enable a cost-effectiveness comparison. Does the Committee consider it is a relevant comparator?
- What does the Committee consider to be the likely sequence of treatments in BRAF positive and BRAF negative melanoma if ipilimumab was a first line option?
- The manufacturer's submission presents a mixed treatment comparison and indirect comparisons of ipilimumab, vemurafenib and dabrafenib. The ERG did not consider this appropriate because the trial populations were not comparable and

dabrafenib is not current standard care in England. Does Committee consider there is sufficient data to compare ipilimumab with vemurafenib and dabrafenib in BRAF V600 mutation-positive patients?

- Given the analyses presented by the manufacturer, including mixed treatment and indirect comparisons and pooled analyses, what does the Committee consider to be a plausible estimate of the size of clinical effectiveness for ipilimumab 3mg/kg alone compared with dacarbazine and with vemurafenib?
- The manufacturer stated that ipilimumab meets NICE's requirements for end-of-life criteria. Does Committee agree with this?

Cost effectiveness

- The ERG stated that the treatment sequencing approach adopted by the manufacturer led to arbitrary assumptions to model second and third lines of treatment. Does the Committee consider it more appropriate to model only first-line treatment?
- If a treatment sequencing approach is preferred, the ERG stated that overall survival and progression-free survival for second-line ipilimumab from Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (NICE technology appraisal 268) could be applied directly in the model. Does the Committee consider this to be appropriate despite the complexity it would involve?
- The manufacturer used data from the vemurafenib arm of the BRIM-3 trial for comparing ipilimumab with vemurafenib. Does the Committee consider this to be acceptable in the absence of robust comparative evidence, or would data from the mixed treatment and indirect comparisons, explored by the ERG, be preferable despite their limitations?
- The ERG explored the impact of different assumptions regarding overall survival on second- and third-line treatment on cost-effectiveness estimates. Which of these assumptions does the Committee consider to be more plausible?
- The ERG examined alternative assumptions to estimate the survival benefit of ipilimumab 3 mg/kg alone, adjusting overall survival curves from the CA184-024 trial based on results from a pooled analysis as well as the hazard ratio from the MDX010-08 trial for ipilimumab plus dacarbazine compared with ipilimumab alone

to account of the impact of concomitant dacarbazine. Does the Committee think this is appropriate?

- The manufacturer's base case suggested an incremental cost-effectiveness ratio (ICER) of £31,559 per QALY gained for ipilimumab compared with dacarbazine in BRAF V600 mutation-positive patients, an ICER of £16,958 per QALY gained in BRAF V600 mutation-negative patients and ipilimumab dominated vemurafenib in BRAF V600 mutation-positive patients. The ERG's preferred ICER estimates ranged from £331,091 to £674,144 per QALY gained for ipilimumab compared with dacarbazine and ipilimumab was dominated by vemurafenib. Which ICERs does the Committee consider to be most plausible?

1 Background: clinical need and practice

1.1 Cutaneous melanoma is a malignant cancer of the skin which in its early stages is normally asymptomatic and, if detected early, before it has spread, can be curable. At presentation, approximately 10% of cutaneous melanomas will have metastasised. Melanoma can spread to nearby lymph nodes (stage III, advanced) or to other parts of the body (stage IV, metastatic).

1.2 It occurs more commonly in fair-skinned people and there is strong evidence that ultraviolet exposure is causal. People with an above-average mole count, sun-sensitive skin, or a strong family history of melanoma are at greatly increased risk. The incidence of malignant melanoma is increasing in England and Wales with rates doubling approximately every 10-20 years. There were 10,656 new diagnoses of malignant melanoma in 2010. In the UK, melanoma is diagnosed at a mean age of around 50 years but approximately 13% of cases occur in young adults aged between 15 and 39 years old. In the UK in 2011 there were 2209 deaths from malignant melanoma (59% in men and 41% in women).

1.3 The best opportunity for cure is by surgical resection of the tumour but only a very small minority of people with advanced disease can still have

their tumour removed. People with unresectable malignant melanoma have a short-term life span and many only receive first-line treatment. People with unresectable stage III or metastatic stage IV disease are usually managed by a specialist oncologist and first line standard care normally involves the administration of chemotherapy with dacarbazine. Radiotherapy, immunotherapy and combination chemotherapy have also been studied in randomised controlled trials. The Melanoma (BRAF V600 mutation positive, unresectable metastatic) - vemurafenib (NICE technology appraisal 269) recommends the BRAF inhibitor vemurafenib as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma, if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme. Dabrafenib monotherapy and in combination with trametinib is currently undergoing appraisal by NICE melanoma appraisal recommends ipilimumab as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.

2 The technology

2.1 Ipilimumab (Yervoy, Bristol-Myers Squibb) is a fully human antibody that binds to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a molecule expressed on T-cells that plays a critical role in regulating natural immune responses. Ipilimumab is designed to block the activity of CTLA-4 resulting in augmentation and prolongation of the T-cell immune response, thereby sustaining the immune attack on cancer cells. It is administered intravenously and has a UK marketing authorisation ‘for the treatment of advanced (unresectable or metastatic) melanoma in adults’.

2.2 The recommended dose of ipilimumab is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of 4 doses. The summary of product characteristics states that all 4 doses should be administered ‘as tolerated, regardless of the appearance of new lesions or growth of existing lesions’. Comparative trial data, however, is

only available for ipilimumab 10 mg/kg and the manufacturer has assumed clinical equivalence between the 3 mg/kg and 10 mg/kg doses, supported by observational data and also stating that this was supported by the European Medicines Agency (EMA). Please see section 4.8 and 4.11 for further details.

2.3 The summary of product characteristics lists the following adverse reactions for ipilimumab: diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 Ipilimumab is priced £3750 per 10 ml vial (5 mg/ml) or £15000 per 40 ml vial (5 mg/ml) (excluding VAT; 'British national formulary' [BNF] edition 66 (online November 2013)). The manufacturer of ipilimumab has agreed a patient access scheme with the Department of Health, in which a discount on the list price of ipilimumab is offered. The patient access scheme price for a 10 ml vial (5 mg/ml) of ipilimumab is [redacted] and [redacted] for a 40ml vial. The average cost of a course of treatment calculated by the manufacturer, using the patient access scheme (PAS) price, is [redacted]. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem(s)

The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of ipilimumab within its licensed indication for previously untreated unresectable stage III or IV malignant melanoma.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with previously untreated advanced (unresectable or metastatic) malignant melanoma	
Intervention	Ipilimumab	
Comparator(s)	Dacarbazine, vemurafenib (in BRAF V600 mutation-positive patients)	Dacarbazine, vemurafenib (in BRAF V600 mutation-positive patients), dabrafenib

The manufacturer also included dabrafenib as a clinical comparator for BRAF V600 mutation-positive patients because it is licensed for monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation and because NICE guidance is currently in development. The manufacturer did not include dabrafenib as a treatment option in the economic model.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	Overall survival, adverse effects of treatment, health-related quality of life	
Economic evaluation	Cost effectiveness of treatments expressed in terms of incremental cost per quality-adjusted life year.	Cost effectiveness in incremental cost per quality-adjusted life year.
	Time horizon for estimating clinical and cost effectiveness sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Life-time horizon (40 years)
	Costs from an NHS and Personal Social Services perspective	Costs from an NHS and Personal Social Services perspective

3.1 Ipilimumab is being positioned in this appraisal for the first-line treatment of previously untreated unresectable stage III and metastatic stage IV malignant melanoma.

4 Clinical-effectiveness evidence

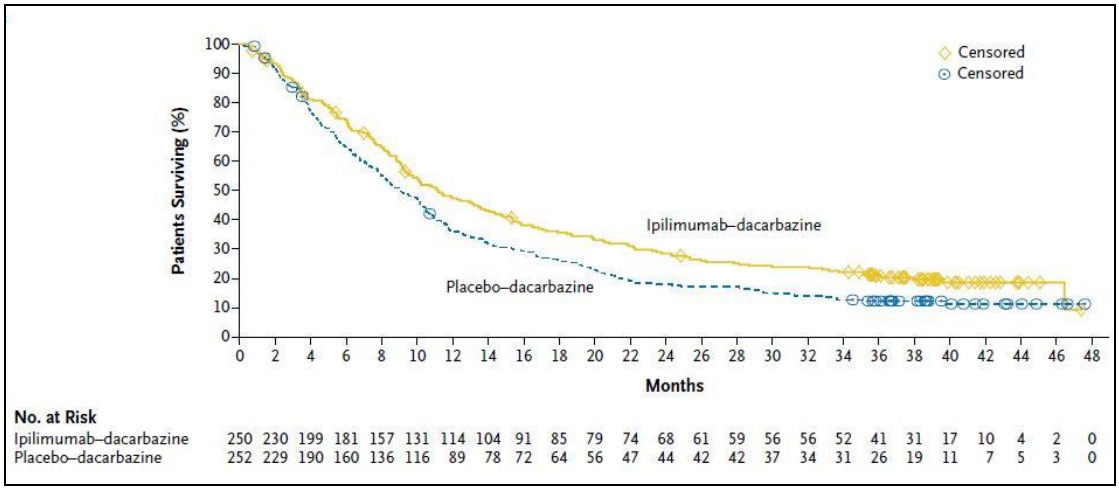
4.1 The manufacturer conducted a systematic literature review and stated that no studies directly comparing ipilimumab 3 mg/kg monotherapy with the comparators specified in the scope (dacarbazine or vemurafenib) were available. However, the manufacturer stated that 4 RCTs identified (CA184-024, MDX010-08, BREAK-3 and BRIM-3) could be used in an indirect comparison of the effectiveness of ipilimumab 3 mg/kg compared with dacarbazine, vemurafenib or dabrafenib. In addition, the manufacturer presented data from 2 ongoing US retrospective, observational studies (CA184-332 and CA184-338) because there was limited RCT evidence directly investigating the clinical efficacy of

ipilimumab 3 mg/kg monotherapy in untreated patients and these studies are conducted with a 'real world' population. An analysis of a pooled chemotherapy-naïve dataset from the CA184-004, MDX010-08, CA184-022 and MDX010-020 trials was also presented to support the use of ipilimumab in the previously untreated setting. Details of the studies and their primary and secondary outcomes are summarised below.

4.2 The CA184-024 study was a multinational, randomised, double-blinded, phase III study observing adults with previously untreated stage III or IV melanoma. The intervention was ipilimumab 10 mg/kg plus dacarbazine, 850 mg/m^2 (n=250) and the comparator was dacarbazine alone, 850 mg/m2 (n=252). Patients were treated with ipilimumab on weeks 1, 4, 7 and 10 and those who were responsive to the treatment received a maintenance phase of ipilimumab therapy or placebo every 12 weeks. The primary outcome was overall survival: median overall survival improved by 2.1 months, from 9.1 months with dacarbazine alone to 11.2 months with ipilimumab plus dacarbazine. The hazard ratio for death was 0.72 (95% CI 0.59 to 0.87, p<0.001), indicating a 28% improvement in overall survival with ipilimumab plus dacarbazine compared with dacarbazine alone. Overall survival rates were higher with ipilimumab plus dacarbazine than dacarbazine 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%). The Kaplan Meier curve demonstrating the overall survival of patients treated with either ipilimumab plus dacarbazine or dacarbazine alone is shown in Figure 1. Secondary outcomes included progression-free survival, overall response rate (complete and partial response), disease control rate (complete or partial response or stable disease), time to response, duration of response, safety and quality of life using the European Organisation for Research and Treatment of Cancer questionnaire (EORTC). There was no statistically significant difference in the median progression-free survival between ipilimumab plus dacarbazine and dacarbazine (2.8 months compared with 2.6 months).

There was a statistically significant decrease in the number of disease progression events (203 compared with 223); with a hazard ratio for progression of 0.76; (95% CI 0.63 to 0.93; p=0.0064) for ipilimumab plus dacarbazine compared with dacarbazine alone. The response rate was statistically significantly improved with ipilimumab plus dacarbazine compared with dacarbazine 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) in the ipilimumab arm. There were no statistically significant differences in disease control rate (which included response and stable disease rates) or time to response or in EORTC QLQ-C30 functioning scales or symptom scales between treatment arms. The trial provided long term clinical and safety profiles with the median follow-up time of greater than 37 months being presented. The follow-up period was 37 months post the last patient enrolment (Table 1).

Figure 1; Kaplan-Meier curve for overall survival of patients enrolled in CA184-024



4.3 The MDX010-08 study was a multicentre, randomised, open-label, phase II, cross-over study carried out in the United States of America, observing adults with unresectable metastatic melanoma who have not received prior chemotherapy and have a life expectancy of greater than 3 months. Treatment was either with the intervention, ipilimumab 3 mg/kg plus dacarbazine 1000 mg/m^2 (n=36) or the comparator ipilimumab 3 mg/kg (n=40). Both groups received ipilimumab on weeks 1, 5, 9 and 13 and

those receiving dacarbazine received this on weeks 1, 4, 7, 10, 13 and 16. The primary outcomes were objective response rate (complete and partial response) and safety. Secondary outcomes included duration of response, length of stable disease, survival, lymphocyte subpopulations and the pharmacokinetics of treatment. The median number of months follow-up in the ipilimumab plus dacarbazine group was 20.9 months and 16.4 months in the ipilimumab alone group. No significant difference was observed for the primary outcome of objective response rate between ipilimumab alone (2/40;5%) and ipilimumab plus dacarbazine (5/36; 13.9%) . The trial demonstrated that there was no statistically significant difference in overall survival between patients who were treated with ipilimumab 3 mg/kg plus dacarbazine and ipilimumab alone. The results appeared to favour ipilimumab plus dacarbazine (median overall survival 14.3 months versus 11.4 months with a hazard ratio for death of 0.75; (95% CI 0.45 to 1.24) and a one year overall survival rate of 62% versus 45%, but the trial was underpowered to detect significant differences in overall survival (Table 1).

4.4 The BREAK-3 study was a multinational, randomised, open-label, phase III, cross-over study observing adults with stage III or IV melanoma who tested positive for the BRAF V600 mutation. People received either dabrafenib 150 mg (n=187) twice daily or dacarbazine 1000 mg/m^2 (n=63) every 3 weeks. The primary outcome was progression-free survival (investigator assessed). The secondary outcomes included progression-free survival (independent review committee assessed), overall survival, objective response rate (complete and partial response), progression-free survival post cross-over, duration of response, quality of life, safety and tolerability by BRAF mutation assay validation. The median length of follow-up was 5 months. The trial was not mature enough to demonstrate a significant difference in overall survival between dabrafenib and dacarbazine. The hazard ratio for death was 0.61 (95% CI: 0.25 to 1.48) for dabrafenib compared with dacarbazine. 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 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 dacarbazine, disease control rate was 91.4% for dabrafenib and 54.0% for dacarbazine (Table 1).

4.5 The BRIM-3 study was a multinational, randomised, phase III, cross-over study observing adults with previously untreated stage IIIC and stage IV melanoma who are also BRAF V600 mutation positive and have a life expectancy of greater than 3 months. People received either vemurafenib 960 mg (n=337) twice a week or dacarbazine 1000 mg/m^2 (n=338) every 3 weeks. The primary outcomes of the trial were overall survival and progression-free survival. The secondary outcomes included confirmed response rate (complete and partial response), time to response, duration of response and the number of people who experienced adverse events. There was an initial and extended follow-up analysis with the initial median months of follow-up for vemurafenib being 3.8 months and 2.3 months for dacarbazine. The extended median months of follow-up were 10.5 months for vemurafenib and 8.4 months for dacarbazine. The trial demonstrated that vemurafenib significantly increased overall survival in BRAF V600 mutation-positive patients when compared with dacarbazine. Median overall survival was increased by 3.6 months (13.2 months versus 9.6 months; HR 0.62; 95% CI 0.49 to 0.77; p<0.001). Overall survival rates were higher with vemurafenib than dacarbazine at six months (84% versus 64%). 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 and hazard ratio for progression 0.26 (95% CI 0.20 to 0.33; p<0.001). The response rate was significantly improved with vemurafenib compared with dacarbazine (48.4% versus 5.5%; p=<0.001), time to response was 1.5 months for vemurafenib, compared with 2.7 months for dacarbazine, although duration of response was not reported (Table 1).

Table 1; Results table for the randomised control trials included in the manufacturer's submission

Randomised control trial	Primary outcome	Secondary outcome
CA184-024	Overall survival rates - higher with ipilimumab plus dacarbazine than dacarbazine 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%)	Median progression-free survival - ipilimumab plus dacarbazine and dacarbazine alone (2.8 months versus 2.6 months). Disease progression events - 203 versus 223; hazard ratio 0.76 (95% CI 0.63 to 0.93; p=0.0064) Response rate - ipilimumab plus dacarbazine compared with dacarbazine alone (15.2% versus 10.3%; P=0.03) Duration of response - ipilimumab plus dacarbazine compared with dacarbazine alone median 19.3 months versus 8.1 months; p=0.03 Disease control rate – no significant difference EORTC QLQ-C30 – no significant difference
MDX010-08	Overall survival – no significant difference between ipilimumab 3 mg/kg plus dacarbazine and ipilimumab alone	
BREAK-3	Progression-free survival -5.1 months for dabrafenib versus 2.7 months for dacarbazine	Response rate - 52.9% for dabrafenib and 19.0% for dacarbazine Disease control rate - 91.4% for dabrafenib and 54.0% for dacarbazine
BRIM-3	Overall survival – 84% versus 64% for vemurafenib and dacarbazine respectively at six months Progression-free survival - 5.3 months versus 1.6 months	Response rate - 48.4% versus 5.5% (p=<0.001) for vemurafenib and dacarbazine respectively Time to response – 1.5 months versus 2.7 months for vemurafenib and dacarbazine respectively

4.6 The CA184-332 (n=61) and CA184-338 (n=120) studies were US multi-site observational retrospective reviews of patient medical records. The aim of both studies was to understand the clinical practice use of ipilimumab 3 mg/kg to treat stage III and IV melanoma in people who were treatment-naive. Treatment was given every 3 weeks for a total of 4 doses. The primary outcomes were demographic and clinical characteristics, occurrence and severity of adverse events and treatment emergent adverse events, patterns of care and overall survival.

Healthcare resource use was the only secondary outcome. The median duration of follow up in the CA184-332 study was 8.5 months and 12 months in the CA184-338 study. The median overall survival for the CA184-332 and CA184-338 observational studies was 11.5 months and 14.3 months, respectively and the estimated one year survival rates were 49% and 60% respectively. BRAF V600 mutation status data was available, and the manufacturer stated that a post-hoc analysis of CA184-338 supports the conclusion from a previous post-hoc analysis of CA184-004 that tumour mutation status does not impact on the clinical activity of ipilimumab with no differences in survival function (p=0.23) observed between BRAF V600 mutation-positive and BRAF V600 mutation-negative patients. The next scheduled analysis is expected to be available at the end of December 2013/ beginning of January 2014 and the manufacturer has indicated that results will include overall survival, adverse events, treatment pathways, patterns of care and resource utilisation based on 1 year follow-up on both cohorts.

4.7 The manufacturer presented a pooled analysis of chemotherapy-naïve patients (n=78) randomized to 3 mg/kg ipilimumab monotherapy in 3 phase II studies, MDX010-08, CA184004, and CA184022, and 1 phase III study, MDX010-20. It was noted that 43/78 patients had received prior immunotherapy. The manufacturer stated the CA184-004 and CA184-022 results alone were inappropriate for inclusion as standalone RCTs because of low patient numbers but highlighted that they demonstrated clinical equivalence between ipilimumab 3 mg/kg and 10 mg/kg doses and support the extrapolation of CA184-024 results to ipilimumab 3 mg/kg monotherapy (see section 4.8). The MDX010-20 trial was a phase III, double-blind study observing patients with advanced (unresectable or metastatic) melanoma who had previously been treated with regimes containing 1 or more of the following: IL-2, dacarbazine, temozolomide, fotemustine or carboplatin. Patients were randomised in 3 groups (3:1:1) who received either 3 mg/kg ipilimumab plus an investigational gp100 peptide vaccine (n=403), 3 mg/kg ipilimumab alone (n=137) or gp100

alone (n=136). Patients were enrolled regardless of BRAF V600 mutation status. Follow-up ranged up to 55 months. The hazard ratio for death between 3 mg/kg ipilimumab alone with gp100 was 0.66 (hazard ratio 95% CI 0.51 to 0.87; p=0.0026). The median overall survival for ipilimumab 3mg/kg monotherapy in this 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%.

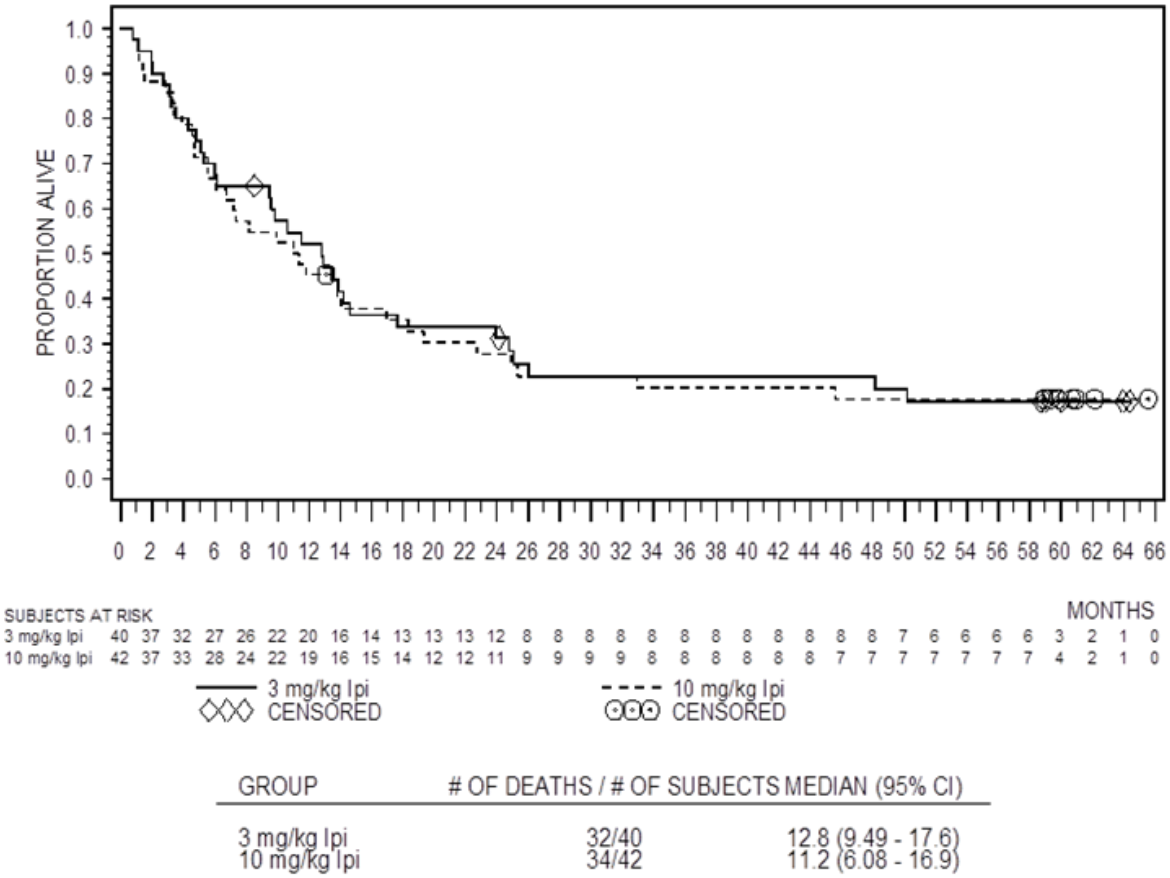
4.8 The manufacturer made several assumptions to support the clinical and cost-effectiveness of ipilimumab 3 mg/kg alone. The first key assumption was that ipilimumab 3 mg/kg and 10 mg/kg were clinically equivalent. Data from 2 trials (CA184-004 (n=40 chemotherapy-naïve patients) and CA184-022 (n=13 chemotherapy-naïve patients) comparing ipilimumab 3 mg/kg and 10 mg/kg were presented in support of this assumption. Both pre-treated and treatment naïve patients were included. The manufacturer carried out preliminary survival analysis on the chemotherapy-naïve subgroups from these 2 trials but stated that this analysis was inappropriate for further discussion because of the low patient numbers. The manufacturer highlighted that the studies indicated that the survival profile of ipilimumab 3 mg/kg and 10 mg/kg was similar with overall survival of 11.2 and 14.3 months respectively. The manufacturer also provided pooled data comparing 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. The Kaplan Meier curves for the pooled data and for CA184-004 are show in Figure 2 and 3. The manufacturer stated that no significant difference in survival was observed between the 3 mg/kg and 10 mg/kg doses of ipilimumab treatment arms in the whole population.

Figure 2; Overall survival profiles for ipilimumab 3 mg/kg and 10 mg/kg; pooled dataset (CA184-022; MDX010-20; CA184-007; CA184-008) Kaplan Meier curve* (taken from manufacturer's clarification responses)

[redacted]

*95% confidence intervals denoted by dashed lines

Figure 3; Overall survival Kaplan Meier curve from CA184-004; total population analysis (taken from manufacturer's clarification responses)



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
3 mg/kg Ipi	32/40	12.8 (9.49 - 17.6)
10 mg/kg Ipi	34/42	11.2 (6.08 - 16.9)

4.9 The second key assumption made by the manufacturer was that ipilimumab plus dacarbazine was equivalent to ipilimumab alone. The manufacturer stated that this was demonstrated in the MDX010-08 trial where ipilimumab 3 mg/kg plus dacarbazine (n=32) provided comparable survival times to ipilimumab 3 mg/kg monotherapy (n=32) after a median follow-up of 20.9 and 16.4 months respectively. Median overall survival times were 14.3 months and 11.4 months and 1 year survival rates were 62% and 45% in the ipilimumab 3 mg/kg plus dacarbazine and ipilimumab 3 mg/kg alone groups respectively. This difference was not statistically significant (p=0.32). The median overall survival with ipilimumab 3 mg/kg alone was directly comparable with that observed with ipilimumab 10 mg/kg plus dacarbazine in CA184-024 (11.4 compared with 11.2 months).

4.10 The manufacturer provided information to demonstrate that ipilimumab efficacy is similar in previously untreated and previously treated patients. The manufacturer stated that the results of the MDX010-20 (previously treated patients) and CA184-024 trials (previously untreated patients) demonstrated similar 2 year overall survival rates 24% and 29% respectively. Although these trials used different regimens (3 mg/kg ipilimumab and 10 mg/kg ipilimumab plus dacarbazine respectively) the manufacturer stated that the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) accepted this evidence from the MDX010-20 trial supported by high level results from the CA184-024 trial as part of the Marketing Authorisation granted in 2011 for ipilimumab for the treatment of adult patients with previously-treated advanced (unresectable or metastatic) melanoma.

4.11 The CHMP commented in the assessment report that ipilimumab 3 mg/kg alone could be supported on the basis of the following considerations:

- The efficacy of 3 mg/kg ipilimumab alone has been established in previously treated melanoma patients; the baseline characteristics of the patients included in the pivotal studies in previously treated and previously untreated subpopulations were similar
- In historical comparisons, ipilimumab 3 mg/kg alone was associated with an increase in median overall survival of at least 2.4 months compared to dacarbazine alone
- Ipilimumab pharmacokinetic data was not significantly affected by concomitant dacarbazine, prior systemic anti-cancer therapy and therefore major differences in exposure between combination treatment and monotherapy or between previously treated patients and previously untreated patients are not expected
- There is no pharmacological or biological rationale to suspect a different activity for ipilimumab treatment in the first or the next line

setting, because the mechanism of action of ipilimumab is general stimulation of the immune-system, which is rather specific

- Concomitant dacarbazine was associated with a markedly increased risk of having hepatobiliary immune-related adverse events (irAEs). The combination of 10 mg/kg of ipilimumab with dacarbazine was associated with treatment discontinuation due to study drug toxicity in 89 (36%) patients, and mean number of doses of 2.9 out of the planned 4 doses in the CA184024 study

However, though the CHMP concluded that sufficient evidence of the efficacy of ipilimumab 3 mg/kg in previously untreated patients was available, the CHMP requested that the manufacturer conduct a study on any relevant difference in efficacy between 3 mg/kg and 10 mg/kg. This investigation is currently ongoing in the phase III trial CA184-169. This trial is due to complete in December 2016 but no preliminary results are available. The manufacturer acknowledged the lack of RCT data demonstrating comparative efficacy for ipilimumab 3 mg/kg.

4.12 Data from 3 (CA184-024, BREAK-3 and BRIM-3) of the 4 RCTs identified were analysed as mixed treatment comparisons to provide a comparison between ipilimumab 10 mg/kg and BRAF inhibitors. The MDX010-08 trial including ipilimumab 3 mg/kg could not be included in the mixed treatment comparison because it did not share a common comparator with any of the other trials. The manufacturer stated that given that ipilimumab 3 mg/kg and ipilimumab 10 mg/kg could be considered equivalent (see sections 4.8), the results of the mixed treatment comparison would also hold for a comparison of ipilimumab 3 mg/kg with BRAF inhibitors. The manufacturer stated that hazard ratios of death from the trials were used to populate the mixed treatment comparison analysis because there were different follow-up times and event numbers across trials. A random effects model was used and treatment effects were assessed using pairwise comparisons. The manufacturer constructed a forest plot of overall survival which demonstrated that while ipilimumab plus

dacarbazine was associated with a statistically significant improvement in survival compared with dacarbazine alone (hazard ratio 0.72; 95% CI 0.55 to 0.95), there were no statistically significant differences for ipilimumab plus dacarbazine compared with vemurafenib (hazard ratio 1.16) or dabrafenib (hazard ratio 1.19). Indirect comparisons using the Bucher equation showed there was no statistically significant difference in efficacy for ipilimumab plus dacarbazine compared with vemurafenib (hazard ratio 1.16; 95% CI 0.86 to 1.56) and dabrafenib (hazard ratio 1.18; 95% CI 0.48 to 2.93). The manufacturer acknowledged the limitations within this analysis, noting that due to the different mechanisms of action for ipilimumab and BRAF inhibitor therapies the Kaplan Meier curve shapes for overall survival vary resulting in hazard ratios which may not be proportional across trials. The manufacturer also commented that the BRAF inhibitor trials included cross-over but the hazard ratios had not been adjusted appropriately and incorporated censoring of patients who crossed over. The hazard ratio of death for dabrafenib compared with dacarbazine was calculated using number of deaths rather than median overall survival analysis. Finally, the manufacturer commented that the main difference in patients enrolled in the clinical trials was their BRAF V600 mutation status and previous treatment.

4.13 Long-term safety data was available from the CA184-024 study which indicated that the safety profile improved with reduced ipilimumab dosing. Severe, serious, drug-related and adverse events leading to drug discontinuation were all more frequent in the ipilimumab 10 mg/kg plus dacarbazine group (96%) than in those patients treated with dacarbazine alone (94%). Discontinuations due to study-drug toxicity led to 37% of patients not receiving all 4 doses of ipilimumab 10 mg/kg induction therapy. Of the patients receiving ipilimumab 77.7% (41.7% were grade 3 or 4 events) experienced an immune related adverse event. The most commonly reported adverse reactions were hepatic related with 17.4% to 20.7% of patients experiencing grade 3 or 4 elevations in liver-function but these reactions were generally reversible. Dermatologic, gastrointestinal,

pyrexia, chills and weight loss were other adverse events observed in the trial. Ipilimumab had a similar safety profile in both patients during the induction period and those treated for longer than 2 years. In the MDX010-08 trial, all patients experienced at least 1 adverse event while in the ipilimumab alone group 53.8% experienced an immune related adverse event whereas in the ipilimumab plus dacarbazine group 65.7% of people experienced an immune related adverse event. Serious adverse events, drug-related adverse events and adverse events leading to drug discontinuation were more frequent in the ipilimumab alone group than in the ipilimumab plus dacarbazine treatment group. One person died from a suspected drug-related adverse event in the dacarbazine alone group. The manufacturer reported that in the CA184-338 study 54.2% of people treated with ipilimumab 3 mg/kg experienced a drug-related adverse event. The manufacturer stated that, overall, dermatologic, gastrointestinal and hepatic adverse events were most common for ipilimumab across trials but these were medically manageable.

4.14 Health-related quality of life (HRQL) was pre-specified as an outcome measure in the CA184-024 trial using the European Organisation for Research and Treatment of Cancer questionnaire (EORTC-QLQ-C30). Baseline questionnaires were completed by 477 patients followed by lower completions rates during the induction, maintenance and follow-up periods of ipilimumab treatment. Of the patient observations recorded using the questionnaire, 62 (2.38%) responses could not be used to generate utility values as data was missing. In 164 (6.3%) of the completed questionnaires, at least one variable was missing. The results suggested that ipilimumab had no significantly negative effect on quality of life, that is, there were no statistically significant differences in emotional functioning, pain, insomnia, constipation, diarrhoea and financial difficulties between treatment arms. Longitudinal comparisons did not show any significant differences in EORTC-QLQ-C30 functioning scales or symptom scales between treatment groups ($p>0.05$). Patient responses were converted from the EORTC-QLQ-C30 to an 8-dimension preference-

based measure, the EORTC-8D. There was no significant difference between the pre- and post-progression EORTC-8D utilities. Heath-related quality-of-life (HRQL) of the patients treated with ipilimumab returned close to baseline following 12 weeks of induction therapy and was maintained beyond treatment. Quality of life, in terms of utility, remained close to the age matched general population for patients who survived at least an additional 6 months with ipilimumab therapy. BREAK-3 and BRIM-3 trials also both measured HRQL. The BRIM-3 trial used the Functional Assessment of Cancer Therapy Melanoma questionnaire to measure health-related quality-of-life but due to low completion rate the data was not reported.

4.15 The ERG stated that the manufacturer had identified all relevant RCTs with adequate study details being included in the submission. The ERG was satisfied that the CA184-024 trial was a large, good quality trial but stated that it did not provide direct evidence for the effectiveness of ipilimumab 3 mg/kg monotherapy (without maintenance therapy) compared with dacarbazine, vemurafenib or dabrafenib for treating previously untreated, advanced melanoma. The ERG noted that the MDX010-08 trial included treatment every 3 weeks rather than every 4 weeks as per the marketing authorisation and also stated that the trial was under powered to detect a significant difference in overall survival. The ERG stated that the BREAK-3 and BRIM-3 trials for dabrafenib and vemurafenib were of reasonable quality, although they were both open-label and had relatively short follow-up periods.

4.16 The ERG commented that the non-RCT studies were generally adequate although there is a high risk of bias with this study design and the ERG were of the opinion that these studies did not provide additional relevant reliable data. In particular, the ERG stated that the pooled analysis of chemotherapy-naïve patients could result in double counting since the MDX010-08 trial was also included independently. The ERG highlighted that there were differences in performance status, disease stage, presence of brain metastases, duration of melanoma and prior

immunotherapy across the 2 observational studies and the pooled analysis and, additionally, it was inappropriate to compare the results of these studies with the dacarbazine alone arm of the CA184-024 trial because of differences in study design and patient characteristics.

4.17 The ERG disagreed with the manufacturer's assumption that 3 mg/kg and 10 mg/kg doses of ipilimumab have equivalent clinical effectiveness. The ERG stated that the manufacturer cited the CA184-022 and CA184-004 trials to support this assumption whereas these trials were not included in the systematic review. Additionally, the ERG highlighted that survival was better with ipilimumab 10 mg/kg in the CA184-022 (n=18) trial though this improvement was not statistically significant (hazard ratio 0.875; 95% CI 0.593 to 1.291) and overall response rate was statistically significantly improved with ipilimumab 10 mg/kg while grade 3 or 4 adverse events were more common at the higher dose. The ERG noted that the though CA184-004 trial indicated no meaningful differences with different doses of ipilimumab, the numbers in this study were very small (n=36). In response to clarification the manufacturer presented results of a pooled analysis which compared overall survival profiles of ipilimumab 3 mg/kg from the MDX010-20 and CA184-022 studies and 10 mg/kg from the CA184-007, CA184-008 and CA184-022 studies for a mixed population of both previously treated and untreated patients. The ERG stated that 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 (Figure 2) and that methods for pooling had not been presented and the ERG was unable to confirm the reliability. The ERG also noted that this analysis included primarily previously treated patients. The ERG stated that the US Food and Drugs Administration (FDA) and European Medicines Agency (EMA) both commented on that lack of evidence for the most clinically effective dose of ipilimumab and there is currently an ongoing trial, CA184-169, comparing 3 mg/kg and 10 mg/kg doses of ipilimumab.

4.18 The ERG also disagreed with the manufacturer's assumption that ipilimumab alone and ipilimumab plus dacarbazine have equivalent

clinical effectiveness. The ERG did not agree with the manufacturer that the MDX010-08 trial provided evidence of equivalence between ipilimumab monotherapy and ipilimumab plus dacarbazine, noting that the hazard ratio for death with ipilimumab plus dacarbazine was 0.75 (95% CI 0.45 to 1.24) compared with ipilimumab alone and highlighting that the trial included only 64 patients and was underpowered to detect a statistically significant difference in overall survival.

4.19 The ERG stated that it did not consider the indirect comparisons and mixed treatment comparisons conducted by the manufacturer appropriate, largely because of the differences in patient baseline characteristics. The patient populations in the CA184-024, BREAK-3 and BRIM-3 trials differed with the latter 2 restricted to patients who were BRAF V600 positive. 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 noting that these are prognostic factors associated with poorer outcomes. Additionally, the ERG also noted the difference in study designs and the difference in the mechanism of action between ipilimumab and the BRAF inhibitors resulting in a violation of the proportional hazards assumption. Therefore the ERG stated that there was no reliable clinical effectiveness evidence for a comparison of ipilimumab with vemurafenib. Based on its concerns noted above, the ERG stated that the survival benefit associated with ipilimumab 3 mg/kg was likely to be overestimated in the manufacturer's submission.

5 Comments from other consultees

5.1 The professional groups and clinical specialists confirmed that ipilimumab is currently given to people with advanced melanoma only after failure of previous therapy and stated that there was strong support for ipilimumab as a first line treatment option for both BRAF V600 mutation-negative and positive patients with advanced, inoperable melanoma. It was highlighted that current standard practice in this setting is dacarbazine, which has a response rate of only 10 to 20%. The professional groups reported

estimates from pooled data on 1861 patients treated with ipilimumab in 12 prospective studies which indicated that the median overall survival with ipilimumab was 11.4 months, with a 7 year overall survival rate of 17%. They stated that responses to ipilimumab treatment can be slower than to chemotherapy and may be seen after the induction period. The professional groups also stated that there is evidence that patients who have smaller volume disease may be more likely to respond and that earlier treatment would give them the time to respond. Therefore, the clinical community supported ipilimumab for first-line treatment of stage 4 melanoma, especially for BRAF V600 mutation-negative patients unable to benefit from vemurafenib or other BRAF inhibitors. It was also noted that vemurafenib was likely to remain the standard practice for people with BRAF V600 mutation-positive disease. In addition, a professional group stated that BRAF V600 mutation-negative patients with rapidly progressing disease might be offered cytotoxic chemotherapy or experimental treatment instead as they may struggle to cope with the potential side effects of ipilimumab. These side effects include severe immune related toxicities and have less opportunity to benefit from immunotherapy due to a shorter life expectancy.

5.2 The professional groups stated the pivotal trial compared ipilimumab plus dacarbazine with dacarbazine alone, but noted that dacarbazine is thought to have contributed little to the trial outcome, so there is an expectation to use ipilimumab monotherapy first line, not in combination with dacarbazine. It was also noted that ipilimumab has been associated with immune related side effects which can be severe and potentially life threatening in around 10% of patients and 1 in 10 may require hospitalisation. These side effects were identified in clinical trials and from this algorithms were formulated to manage toxicity and deaths due to ipilimumab although these are rare in practice. Implementation was not thought to be an issue because staff are already trained to use this treatment. It was considered that the technology would not impact on equality issues.

5.3 The patient groups stated that advantages of ipilimumab treatment for melanoma include increased potential for long term survival, improved quality of life, increased treatment choice and hope for patients. In particular, ipilimumab could provide another treatment option for BRAF V600 mutation-negative patients who do not have the option of vemurafenib treatment. One patient detailed how they experienced immediate response when their melanoma was treated with ipilimumab, with a rapid reduction in skin lesions and discomfort whereas previous dacarbazine treatment had little effect. The patient was able to return to normal working post treatment once the side effects had subsided and has been cancer free for 7 years. The patient groups and patient expert noted some disadvantages to treatment with ipilimumab including nausea, vomiting, diarrhoea and abdominal pain but stated that these were tolerable given the potential benefit, and could be proactively managed.

6 Cost-effectiveness evidence

6.1 The manufacturer conducted a systematic review but did not identify any relevant cost-effectiveness studies including ipilimumab for previously untreated advanced unresectable malignant melanoma. The manufacturer therefore conducted a de novo analysis to estimate the cost-effectiveness of ipilimumab compared with dacarbazine in BRAF V600 mutation-negative patients, and compared with dacarbazine and vemurafenib in BRAF V600 mutation-positive patients. The manufacturer developed a semi-Markov partitioned survival model with health states used to represent tiers of treatment, incorporating second-line active therapy and third-line best supportive care (Figure 4). The lines of treatment included for each sub-population is depicted in Figure 5. The manufacturer stated that this approach reflected the pattern of care routinely provided in UK clinical practice and took into account the costs and outcomes associated with each line of treatment.

Figure 4; Simplified economic model structure

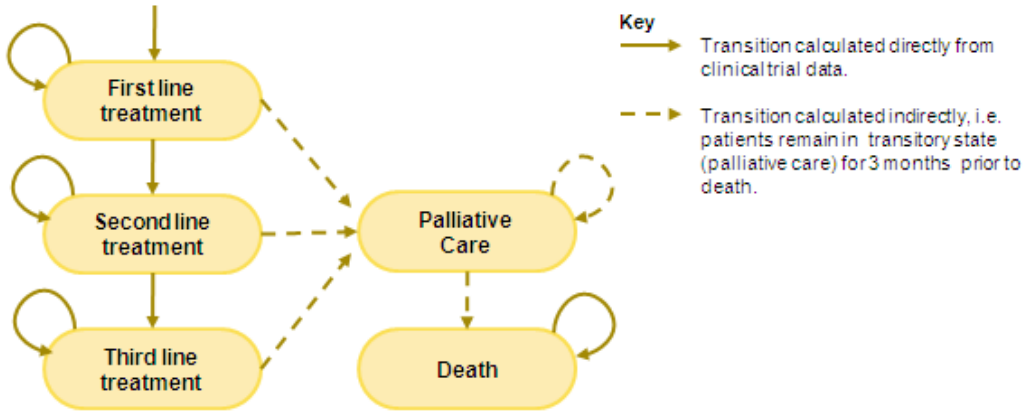
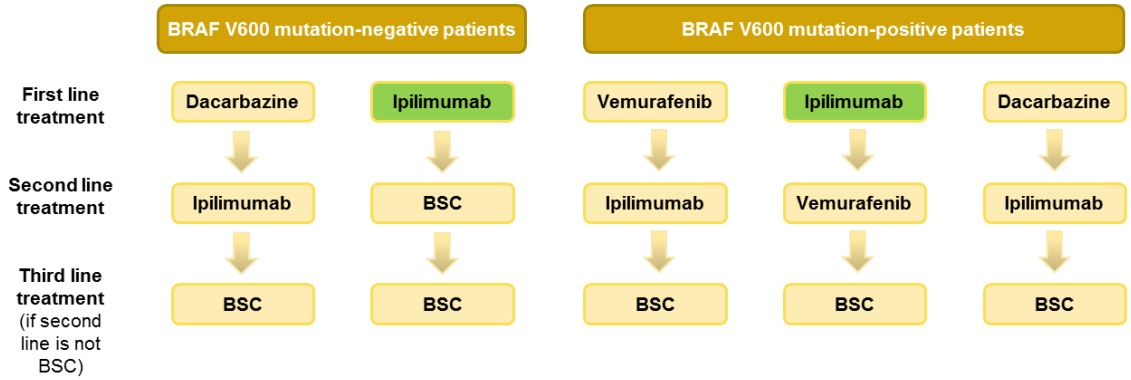


Figure 5; Modelled treatment patterns



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

6.2 The proportion of patients moving between health states was derived by initially calculating the number of patients who died and then adjusting the proportion of patients at each line of treatment by those who would be expected to receive palliative care (defined as 12 weeks prior to death). The model maintains the per-cycle risk of death to be equal for ipilimumab, dacarbazine and vemurafenib and for the patients entering palliative care to be a proportion of patients in each treatment group. The base-case included a lifetime time horizon of 40 years, a cycle length of 1 week and a discount of 3.5% for costs and utilities.

6.3 The manufacturer distributed patients across 6 health states, each associated with a utility value, and 6 time-to-death sub-health states, to

capture quality of life as a function of time to death. In the base case model a utility decrement for people treated with ipilimumab or vemurafenib was included to account for treatment-related adverse events. There was no separate reduction in quality of life resulting from the adverse events applied in the model. Patient health-related quality-of-life (HRQL) was estimated from time to death as an intermediate outcome as the manufacturer determined this to be the most meaningful way of estimating HRQL, as disease progression. The manufacturer stated that due to adverse events in the induction period not all patients would receive all 4 induction doses of ipilimumab as demonstrated in the CA184-024 trial. 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.

6.4 There was no direct evidence for the clinical effectiveness of ipilimumab 3 mg/kg alone compared with dacarbazine or vemurafenib for the treatment of previously untreated, advanced melanoma patients. The manufacturer included efficacy, adverse event and health-related quality-of-life (HRQL) data for ipilimumab 10 mg/kg plus dacarbazine compared with dacarbazine alone from the CA184-024 trial, making the assumption that ipilimumab 10mg/kg was equivalent to ipilimumab 3 mg/kg (see section 4.8). The manufacturer also concluded that ipilimumab plus dacarbazine had the same effectiveness as ipilimumab alone as demonstrated in the MDX010-08 trial where ipilimumab 3 mg/kg plus dacarbazine and ipilimumab 3 mg/kg alone demonstrated comparable overall survival (section 4.9). The manufacturer also assumed that the efficacy of ipilimumab in BRAF V600 mutation-positive and –negative patients was equivalent. The manufacturer justified this by stating that a post-hoc analysis of a subgroup containing 69 people from the CA184-004 trial indicated there was no difference in objective response and stable disease based on the BRAF V600 mutation status.The

manufacturer also presented an analysis using the pooled chemotherapy-naïve dataset analysis (CA184-004, MDX010-08, CA184-022 and MDX010-020), stating that overall and progression-free survival outcomes were similar using the two datasets. For vemurafenib, the manufacturer stated that there was no difference in the dacarbazine arms of the CA184-024 and BRIM-3 trials and therefore data from the vemurafenib arm of the BRIM-3 trial was incorporated directly into the model. The breakdown of treatments comprising best supportive care and the median duration of best supportive care was taken from the MELODY study.

6.5 The transition to second- and third-line treatment was modelled based on progression-free survival data, while overall survival data was used to model transition to death. For first-line ipilimumab and dacarbazine therapy, the manufacturer fitted a 3 part survival curve, consisting of Kaplan–Meier data from the CA184-024 trial for 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. A 2 part curve fit was used to extrapolate progression-free data over a lifetime horizon, consisting of Kaplan–Meier data up to 12 weeks followed by a Weibull survival function for patients progression-free at week 12. For first-line vemurafenib therapy, the manufacturer fitted Kaplan–Meier survival data from the BRIM-3 trial up to 14 months, followed by 3 different monthly risks of death between months 14 and 46. For patients alive at month 46, a Weibull distribution was fitted to AJCC registry data from year 4 to year 5, while a separate Weibull distribution was fitted to AJCC registry data from year 5 onwards. For extrapolating progression-free survival, the manufacturer fitted Kaplan–Meier data from the BRIM-3 trial for up to 9 months, which was followed by a monthly risk of progression thereafter. For second-line treatments, overall survival 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 survival with second-line ipilimumab. 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 best supportive care, which consisted of a proportion of patients on 'no treatment' and a proportion on commonly prescribed chemotherapy drugs, including dacarbazine. The overall survival for patients receiving third-line best supportive care was assumed to be the same as those on first-line treatment who had not progressed to next line of therapy. The manufacturer highlighted that for patients treated with ipilimumab, using progression-free survival overestimates the number of patients moving to second-line treatment because it is possible for patients to initially progress and then become stable or respond to therapy due to its mode of action. This may cause overestimation the cost on the ipilimumab arm because costs of first-line treatment with ipilimumab are almost static whereas the costs of second-line treatment depend on the time spent on treatment.

6.6 In the base case, the manufacturer used a 'method of moments' calculation to estimate the costs associated with ipilimumab. Using patient level data from the UK patients in the CA184-024 trial and the ipilimumab compassionate use programme (n=258), the average number of vials required was calculated. The cost of ipilimumab was calculated to be [redacted] and an administration fee of £285 was also incorporated. An additional £1.23 was added each time ipilimumab was administered to account for liver and thyroid function tests. The cost of vemurafenib was presumed to be 4 packs of tablets every 4 cycles as in NICE TA269 Melanoma (BRAF V600 mutation positive, unresectable metastatic) - vemurafenib (NICE technology appraisal 269), which was calculated to be [redacted] as well as an administration fee of £138. The costs of dacarbazine and best supportive care were calculated based on an average height (170 cm) and weight (78.65 kg) for the patients, taken from the CA184-024 trial. Dosing schedules for dacarbazine and best supportive care were taken from product summary of product characteristics (SPCs) and in the base case the number of vials required was rounded up to the nearest vial. The cost of dacarbazine was calculated as £53.66 and an

administration fee of £284. The dose and costs of dacarbazine were considered equal in the first-line and best supportive care setting. The same patient access scheme (PAS) will be in place as agreed in Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (NICE technology appraisal guidance 268). When calculating the costs of treatment in the manufacturer's base case both the ipilimumab and vemurafenib PAS prices were used and are therefore confidential.

6.7 Second-line costs for ipilimumab were taken from the previous NICE appraisal for ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. The average administration cost for second-line ipilimumab treatment was £32.84 and the average drug cost per cycle was [redacted] which was adjusted proportionately to the difference in average weight between the CA184-024 clinical trial and the second-line evaluation, using a multiplier of 0.9977. The per cycle drug cost was calculated to be [redacted] for second-line ipilimumab treatment. The administration and drug costs for second-line vemurafenib treatment were assumed to be equal to first-line costs. To account for the wastage incorporated in the costs for first-line vemurafenib treatment, an additional 5.78% was added to the drug cost. The total drug cost per cycle for second-line vemurafenib was [redacted]. The best supportive care costs were applied to patients in the first 7 cycles of best supportive care for both second- and third-line therapy, based on the median duration of 6.6 weeks of treatment from the MELODY study.

6.8 The manufacturer included one off resource costs such as treatment initiation, progression to a new line of therapy and terminal care which was applied at death as well as per cycle costs including treatment and those receiving palliative care. Table 2 summarises these costs included in the model.

Table 2; Resource use

Line of treatment/ health state	Total cost
First-line treatment initiation	£955.03
Receiving first- or second-line treatment	£60.24
Initiation of subsequent treatment lines	£1,354.38
Patients not receiving treatment	£115.09
Receiving palliative care	£384.23
Terminal care – applied on death	£6,177.20

6.9 For BRAF V600 mutation-positive patients, base-case results indicated that vemurafenib was dominated by ipilimumab because it was associated with higher costs and fewer QALYs. Following from this, a comparison of ipilimumab with dacarbazine resulted in an ICER of £31,559 per QALY gained using the CA184-024 results (Table 3) and £28,465 per QALY gained when using the pooled chemotherapy-naive data for ipilimumab. For BRAF V600 mutation-negative patients, the ICER for ipilimumab compared with dacarbazine was £16,958 per QALY gained using the CA184-024 study results (Table 4) and £17,866 per QALY gained using the pooled chemotherapy-naïve data. The manufacturer stated that the ICERs were lower in the BRAF negative group because as no costs for vemurafenib second line were involved.

Table 3; Base case results, CA184-024 data for ipilimumab – BRAF V600 mutation-positive (incremental pairwise comparison with ipilimumab)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	Incremental analysis
Dacarbazine	£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 4; Base case results, CA184-024 data for ipilimumab – BRAF V600 mutation-negative

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER

Dacarbazine	£44,267	2.1476	1.5570			
Ipilimumab	£57,760	3.3522	2.3527	£13,492	0.7956	**£16,958**

6.10 A variety of curve fits were tested in the sensitivity analyses of the data in the model developed using the CA184-024 trial data. The manufacturer conducted one-way deterministic sensitivity analysis using a tornado diagram to assess the impact of key uncertainties on the ICERs and probabilistic sensitivity analyses using 1000 simulations (Table 5). The probabilistic sensitivity analyses took into account all parameters whereas the deterministic sensitivity analysis did not include drug costs or the proportion of patients experiencing adverse events from best supportive care. Sensitivity analysis was only carried out for the BRAF V600 mutation-positive population because the ICER for ipilimumab compared with dacarbazine was higher for this group and was therefore considered the worst case scenario.

Table 5; Results of the probabilistic sensitivity analysis (mean over 1000 runs)

Ipi data source	Ipilimumab		Vemurafenib		Dacarbazine		ICER vs. vemurafenib	ICER vs. dacarbazine
	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**

6.11 The manufacturer used two different maximum acceptable ICERs to calculate the incremental net benefit; £30,000 per QALY when comparing with vemurafenib and £50,000 per QALY when comparing with dacarbazine. The deterministic sensitivity analysis indicated that the model was most sensitive to the parameters used to model overall survival for ipilimumab and dacarbazine, the time spent on second line treatment and the time spent on first line treatment with ipilimumab compared with dacarbazine. Tornado diagrams depicting the incremental net benefits are presented on page 194 and 195 of the manufacturer's submission. The manufacturer stated, after carrying out probabilistic

sensitivity analysis (PSA), that the probability of ipilimumab being cost effective when compared with dacarbazine was 96%, using £50,000 as the maximum acceptable ICER. At a threshold of £30,000 per QALY the probability of ipilimumab being cost-effective is 40%. The manufacturer also performed a scenario analysis which suggested that the ICERs were insensitive to changes in the structural assumptions including the source of clinical data and how survival was modelled. The manufacturer suggests that the most pessimistic ICER for ipilimumab compared with dacarbazine was £49,579 per QALY gained, assuming a single parameter curve fit using a lognormal distribution for overall survival. However, the manufacturer emphasised that single parametric curve fits were a poor fit to the data and proportional hazards was not present between ipilimumab and dacarbazine, so this did not represent a realistic scenario.

6.12 The ERG stated that the manufacturer's systematic review was appropriate and did not identify any relevant cost-effectiveness analyses of ipilimumab for previously untreated unresectable malignant melanoma. The ERG was satisfied that the de novo analysis conducted by the manufacturer was in line with the decision problem and NICE reference case. The ERG expressed some major concerns about the assumptions in the manufacturer's model, particularly about the relative efficacy data used in the model. The ERG stated that it was inappropriate to assume that ipilimumab 3 mg/kg was clinically equivalent to ipilimumab 10 mg/kg (see section 4.8) or that ipilimumab plus dacarbazine was equivalent to dacarbazine alone (see section 4.9) and therefore stated that using data from the CA184-024 trial could not be fully justified. The ERG also highlighted that using data only from the vemurafenib arm of the BRIM-3 trial for comparing ipilimumab with vemurafenib was inappropriate because it broke randomisation and raises concerns about the exchangeability of populations across the trials. The ERG noted the problems with the mixed treatment comparison conducted by the manufacturer (see section 4.12), but stated that the results of this analysis should have been used to check consistency of results, highlighting that

using the independent arm from the BRIM-3 trial directly favoured ipilimumab.

6.13 The ERG raised concerns around the treatment sequencing approach used to structure the model, stating that the existing evidence for ipilimumab does not include a comparison of sequential use of treatments for previously untreated advanced melanoma. The ERG stated that this model structure resulted in oversimplified assumptions about overall and progression-free survival on second- and third-line treatments. The ERG was unclear why the manufacturer did not attempt to use the overall survival and progression-free survival for second-line ipilimumab used in the previous ipilimumab appraisal Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (NICE technology appraisal 268). It noted in the manufacturer's clarification that the incorporation of the time-dependent overall survival and progression-free survival curves from NICE's advanced melanoma (TA268) technology appraisal 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. The ERG acknowledged the additional complexity but emphasised that if the manufacturer's preferred choice was to model the sequencing of treatments, then the additional complexity required to implement the sequencing of treatments must be incorporated. This incorporation must occur in both the model and methods such as adding a series of sub-health states (tunnel states) to model time to progression explicitly could have been implemented. The ERG stated that the methods to model first-line overall and progression-free survival were appropriate but highlighted that given that the population under consideration is highly heterogeneous, the statistical approach should be supported by the clinical plausibility of a change in hazard at a particular time point.

6.14 The ERG was satisfied with the individual treatment pathways but had concerns relating to the set of assumptions used to model survival for the different lines of treatment. Patients who received ipilimumab as first-line treatment were assumed to follow the overall survival curve from the CA184-024 trial until progression. When the patients move to best supportive care the model assumes that patients continue to follow the ipilimumab overall survival curve from the CA184-024 trial until they die. The ERG stated that this would indicate a sustained overall survival benefit from first-line ipilimumab. The ERG also had concerns about the contrasting method used to model overall survival for the comparator treatments. Patients receiving dacarbazine as first-line treatment were assumed to follow the dacarbazine overall survival curve from the CA184-024 trial until progression to ipilimumab. The overall survival for these patients was based on a downward adjustment of the first-line overall survival curve for ipilimumab (hazard ratio = 1.21). Once patients move onto best supportive care the model assumed the patient followed the overall survival curve of first-line dacarbazine. The ERG stated that this switching between overall survival curves was arbitrary and the manufacturer had not supplied any support for the assumption that patients receiving first-line ipilimumab maintained sustained benefit of overall survival long term while patients receiving ipilimumab second-line did not. The ERG commented that this approach favoured ipilimumab.

6.15 The ERG stated that the modelled treatment pathways for BRAF V600 mutation-positive patients demonstrated similar inconsistencies in the use of overall survival curves. Patients who received ipilimumab as first-line therapy followed the overall survival curve from the CA184-024 trial. At the point of progression, modelled using the progression-free survival curve from the CA184-024 trial, patients switch to vemurafenib. Patients then follow the overall survival curve for second-line vemurafenib, based on a downward adjustment of the first-line vemurafenib curve from the BRIM-3 trial. When patients switch to third-line best supportive care they are assumed to follow the overall survival of first-line ipilimumab without

any adjustment of the curve. The ERG stated that this switch was difficult to justify and unlikely to be supported by clinical evidence.

6.16 The ERG had concerns around the health-related quality-of-life (HRQL) data and the approach the manufacturer had used to model HRQL outcomes. The manufacturer used utility values derived from the EORTC QLQ-C30 questionnaire completed in the CA184-024 trial, using the Rowen algorithm. The ERG had concerns that no direct EQ-5D data was collected and that the Rowen algorithm may not be sufficiently generalisable to the current appraisal population. The manufacturer claimed that the utility values used in the submission were consistent with the utilities in the submission for second-line ipilimumab treatment but the ERG disagreed with this as the utility values in the previous appraisal were based on progression rather than proximity to death. The ERG was also concerned about the progressively lower completion rates of EORTC QLQ-C30 among surviving patients at subsequent points in time which could reflect selection bias. The ERG requested clarification on the reasons for non-completion but this was unavailable. The ERG also noted that the utilities did not capture positive treatment effect.

6.17 The ERG stated that the analysis and modelling conducted by the manufacturer favoured ipilimumab and that an alternative model structure based on first-line treatment only was more plausible. The ERG noted the ability to ‘turn off’ the treatment sequencing to allow for direct comparison between the first-line ipilimumab and dacarbazine treatments in terms of overall survival and progression-free survival. When observing the manufacturers scenario analysis the ERG considered the ‘no active second-line treatments’ to be the most important as this represents the stage model for pre- and post-progression and death. The only second-line treatment is best supportive care. The resulting ICER for comparison between ipilimumab and dacarbazine increased from £31,559 to £42,449 and when comparing to vemurafenib the ICER was no longer dominant and became £28,980 in the BRAF V600 mutation-positive population.

ERG's exploratory analysis

6.18 The ERG conducted several exploratory analyses to explore the concerns identified with the manufacturer's model. Firstly, the ERG explored the impact of different assumptions regarding overall survival on second- and third-line treatment on cost-effectiveness estimates. For the BRAF V600 mutation-negative population, the ERG presented 3 scenarios: scenario 1, which the ERG stated was most plausible, assumed that for the dacarbazine arm, overall survival for best supportive care was modelled by assuming that patients remain on the same overall survival curve of second-line treatment, which was consistent with the assumption used for the ipilimumab arm in the manufacturer's model; this increased the ICER for ipilimumab compared with dacarbazine from £16,958 to £18,833 per QALY gained (see Table 6). In scenario 2, the ERG assumed the overall survival curve of ipilimumab second-line for best supportive care, and in scenario 3 the overall survival curve of dacarbazine first-line was assumed for best supportive care. The resulting impact on the ICER was to increase it to £40,005 per QALY gained and £56,486 per QALY gained respectively. Similar analyses for the BRAF V600 mutation-positive patients, resulted in an increase in the manufacturer's base-case ICER compared with dacarbazine from £31,559 to between £71,335 and £941,091 per QALY gained (Table 6). In the manufacturer's base case ipilimumab dominated vemurafenib in the BRAF V600 mutation-positive population but moved to the south-west quadrant of the cost-effectiveness plane with an ICER between £27,180 and £84,980 per QALY gained (Table 7). The ERG stated that this exploration highlighted the sensitivity of the manufacturer's analysis to the modelling of overall survival and emphasised that a model structure with only first-line treatments was more appropriate. The ERG therefore turned off the sequential use of treatments in the manufacturer's model so that it followed a conventional three-state cancer model with the only additional line of therapy being that of best supportive care. The ERG noted that the manufacturer had also presented the results from a similar analysis assuming patients did not

receive any second-line therapy which resulted in an ICER of £42,449 per QALY gained for ipilimumab compared with dacarbazine for the overall population. The ERG noted that this ICER was based on the assumption that once patients progress to best supportive care, different overall survival curves were followed depending on treatment received at first-line. The ERG, however, also presented an analysis assuming the same overall survival curves for patients who progress to best supportive care resulted in an ICER of £123,676 per QALY gained for ipilimumab compared with dacarbazine. When the same comparison was carried out between ipilimumab and vemurafenib, vemurafenib dominated ipilimumab whereas in the manufacturer's analysis assuming patients did not receive any second line therapy the ICER was £28,980 per QALY. The ERG stated that these ICERs represented the possible extremes.

Table 6; Cost-effectiveness results for different assumptions on OS in second- and third-line for BRAF V600 mutation-negative subgroup; Ipilimumab versus dacarbazine

Scenario			Ipilimumab		Dacarbazine		Inc. Costs (£)	Inc. QALYs	ICER
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Manufacturer's base-case									
	Ipilimumab	Dacarbazine (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
OS for best supportive care, same as 2nd line									
	Ipilimumab	Dacarbazine							
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
Same OS for best supportive care, dacarbazine 1st line OS									
	Ipilimumab	Dacarbazine							
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
Same OS for best supportive care, Ipi 2nd line OS									
	Ipilimumab	Dacarbazine							
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
OS for best supportive care, same as 2nd line									
	Ipilimumab	Dacarbazine							
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

Table 7; 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
			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	Ipilimumab dominates vemurafenib
Same OS for BSC, Vemurafenib 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	Ipilimumab in SW Quadrant £84,980
Sequence of treatment, ipilimumab followed by vemurafenib, vemurafenib followed by ipilimumab									
	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	Ipilimumab in SW Quadrant £27,180

6.19 To further explore the manufacturer's assumption that ipilimumab 3mg/kg was clinically equivalent to ipilimumab 10mg/kg, which the ERG stated overestimated the overall survival benefit for ipilimumab, the ERG examined alternative assumptions to estimate the survival benefit of ipilimumab 3 mg/kg alone. The ERG used the pooled overall survival data provided by the manufacturer in response to clarification. The pooled data for the 3 mg/kg ipilimumab dose came from 2 trials (MDX010-20 and CA184-022) and 10 mg/kg ipilimumab dose data from 3 trials (CA184-

007, CA184-008 and CA184-022) in a mixed population of previously treated and untreated patients. The ERG estimated the implied hazard ratio for 3 mg/kg relative to 10 mg/kg by digitising the Kaplan-Meier curves for both doses over the 70 month period (Figure 6). The implied hazard ratio for 3 mg/kg ipilimumab was [redacted] and this was applied to the 10 mg/kg ipilimumab overall survival curve from the CA184-024 to estimate the overall survival for 3 mg/kg ipilimumab. The ERG stated that that the estimated overall survival curve for 3 mg/kg ipilimumab based on the implied hazard ratio was not far off the actual 3 mg/kg ipilimumab curve. The ERG stated that this adjustment increased the ICER for ipilimumab compared with dacarbazine from £16,958 per QALY gained in the manufacturer's analysis to £59,942 per QALY gained in the BRAF V600 mutation-negative population and from £31,559 per QALY gained to £85,806 per QALY gained in the BRAF V600 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 £56,958 per QALY gained for vemurafenib compared with ipilimumab.

Figure 6;

[redacted]

[redacted]

6.20 Following on from the ERG's critique in section 4.19 that there was no conclusive evidence that ipilimumab alone was as clinically effective as ipilimumab plus dacarbazine, the ERG used the hazard ratio from the MDX010-08 trial for ipilimumab plus dacarbazine compared with ipilimumab alone (hazard ratio=0.75) to explore the cost-effectiveness of ipilimumab alone. The ERG stated that this increased the ICER for ipilimumab compared with dacarbazine from £16,958 per QALY gained in the manufacturer's analysis to £73,615 per QALY gained in the BRAF V600 mutation-negative population and from £31,559 to £97,864 per QALY gained in the BRAF V600 mutation-positive population. For the comparison with vemurafenib, ipilimumab was no longer less costly and more effective as in the manufacturer's base-case analysis, with an ICER of £52,199 per QALY gained for vemurafenib compared with ipilimumab.

6.21 The ERG concluded the manufacturer's use of independent arms from different clinical trials for the indirect comparison analysis of ipilimumab and vemurafenib to have resulted in inconsistent estimates of relative efficacy for ipilimumab with those based on an indirect comparison. The ERG acknowledged the manufacturer's reasons for not including the results from the indirect comparison in the model, including that the hazards were not consistent over time and a single hazard ratio could not

be applied accurately to the entire life expectancy of the patients. However, the ERG stated that the manufacturer's assumption around the exchangeability of trial populations is a strong assumption. The ERG therefore developed an alternative scenario based on the results of the indirect comparison analysis. The ERG estimated the overall survival for vemurafenib by applying the hazard ratio from the indirect comparison to the overall survival of first-line ipilimumab. The results of the indirect comparison showed that ipilimumab was less costly but also less effective than vemurafenib. The ICER was £45,410 for vemurafenib versus ipilimumab.

6.22 The ERG stated that its preferred cost-effectiveness estimates were based on a conventional 3 state model based on only first-line treatment, and also incorporating the adjusted overall survival data. This resulted in an ICER of £331,091 per QALY gained for ipilimumab compared with dacarbazine. The ERG carried out a similar analysis adjusting overall survival for concomitant treatment with dacarbazine and this resulted in an ICER of £674,144 per QALY gained for ipilimumab compared with dacarbazine. When the ERG compared ipilimumab with vemurafenib, vemurafenib dominated ipilimumab in both scenarios.

Table 8; Cost-effectiveness of ipilimumab adjusted for 3 mg/kg and concomitant dacarbazine, taking the three-state model as the ERG's preferred base case; ipilimumab versus dacarbazine

Scenario			Ipilimumab		Dacarbazine		Inc. Costs (£)	Inc. QALYs	ICER
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Three-state model									
	Ipilimumab	Dacarbazine (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	Dacarbazine							
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	Dacarbazine							
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

6.23 The ERG noticed a discrepancy in the cost per weekly cycle of ipilimumab depending on whether treatment was first line ([redacted]) or second line ([redacted]). The ERG explored the effect of this price difference on the cost-effectiveness of ipilimumab treatment stating that there was no clinical reason for the per cycle cost to differ between lines of treatment. The ERG found that the ICER for ipilimumab compared with dacarbazine increased from £16,958 to £25,720 per QALY gained in BRAF V600 mutation-negative patients and from £31,559 to £40,816 per QALY gained in BRAF V600 mutation-positive patients. Ipilimumab still dominated vemurafenib in line with the manufacturer's base-case analysis.

6.24 The manufacturer calculated health-related quality-of-life (HRQL) outcomes using time-to-death utility values rather than pre- and post-progression health states, if a conventional 3 state cancer model had been developed. The ERG explored the impact of modelling the manufacturer's data using a three-state model and compared the estimates of cost-effectiveness with those based on utility values for pre- and post-progression as used in the previous ipilimumab appraisal NICE's advanced melanoma (TA268). The ERG stated that the ICER was less sensitive to the utility value assumptions then other scenarios. The ICER increased from £16,958 to £19,320 for the comparison of ipilimumab with dacarbazine in the BRAF V600 mutation-negative population and £31,559 to £35,717 in the mutation-positive population. Vemurafenib continued to dominate ipilimumab.

End-of-life considerations

The manufacturer stated that ipilimumab may be eligible for appraisal as an 'end-of-life' treatment as follows;

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median survival 6-9 months
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	There is no direct evidence for the effectiveness of 3 mg/kg dose of ipilimumab. The CA184-024 trial of ipilimumab 10 mg/kg plus dacarbazine versus dacarbazine alone produced a mean overall survival increase of 2.1 months (11.2 months versus 9.1 months; p<0.001) However the manufacturer stated 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.
The treatment is licensed or otherwise indicated for small patient populations	The manufacturer estimated that the number of untreated unresectable malignant melanoma patients eligible for treatment with ipilimumab is estimated at 1319 (BRAF V600 mutation-positive n=633, BRAF V600 mutation-negative n=686) in 2014

7 Equality issues

7.1 No equality issues were identified during the scoping process or in the submissions received

8 Innovation

8.1 The manufacturer considers ipilimumab to have an innovative mode of action making it fundamentally different to traditional cytotoxic agents. The manufacturer also commented that ipilimumab does not restrict use depending on BRAF V600 mutation status and consider the treatment to provide superior disease control by having a more durable, longer term survival benefit, than the currently recommended first-line options. Patient experts stated that ipilimumab was highly innovative and could significantly enhance the treatment of patients at an early stage of the treatment pathway.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Ipilimumab for previously treated unresectable stage III or IV malignant melanoma. NICE technology appraisal 268 (2012) Review Proposal date Nov 2014.
- Vemurafenib for the treatment of unresectable locally advanced or metastatic BRAF V600 mutation positive malignant melanoma. NICE technology appraisal 269 (2012). Review Proposal date Nov 2014.

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Melanoma (BRAF V600E mutation positive, unresectable, metastatic) - dabrafenib and trametinib. NICE technology appraisal. Expected publication date September 2014.
- Melanoma (BRAF V600, unresectable, metastatic) – dabrafenib. NICE technology appraisal. Publication date to be confirmed.

Appendix B: European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002213/WC500157027.pdf