NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Ipilimumab is recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the 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 has a UK marketing authorisation 'for the treatment of advanced (unresectable or metastatic) melanoma in adults'. The recommended dose of ipilimumab is 3 mg per kilogram of body weight (mg/kg) administered intravenously over a 90-minute period every 3 weeks for a total of 4 doses.

2.2 The summary of product characteristics lists the following very common 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.

2.3 Ipilimumab is priced at £3750 per 10-ml vial (5 mg/ml) or £15,000 per 40-ml vial (5 mg/ml) (excluding VAT; 'British national formulary' [BNF] edition 67). The manufacturer of ipilimumab has agreed a patient access scheme with the Department of Health, in which a confidential discount on the list price of ipilimumab is offered. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

The Appraisal Committee (section 9) considered evidence submitted by the manufacturer of ipilimumab and a review of this submission by the Evidence Review Group (ERG; section 10).

Manufacturer's original submission

3.1 There were no trials directly comparing ipilimumab 3 mg/kg monotherapy with the comparators specified in the scope (dacarbazine or vemurafenib). The key clinical evidence came from 4 randomised controlled trials (CA184-024, MDX010-08, BREAK-3 and BRIM-3) that were 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 trials (CA184-332 and CA184-338) because there was limited randomised controlled trial evidence directly investigating the clinical efficacy of ipilimumab 3 mg/kg monotherapy in people with previously untreated advanced (unresectable or metastatic) melanoma. The manufacturer also presented a pooled analysis of patients who had not had chemotherapy before (n=78), randomised to 3 mg/kg ipilimumab monotherapy in 4 trials: MDX010-08, CA184-004, CA184-022 and MDX010-020.

3.2 The CA184-024 trial was a multinational, randomised, double-blinded trial observing adults with previously untreated advanced (unresectable or metastatic) melanoma. The intervention was ipilimumab 10 mg/kg in combination with dacarbazine 850 mg/m^2 (n=250), and the comparator was placebo plus dacarbazine alone 850 mg/m^2 (n=252). Treatment with ipilimumab or placebo was provided every 3 weeks for the first 10 weeks followed by 1 dose every 12 weeks from week 24. Treatment with dacarbazine was given once every 3 weeks for 22 weeks until disease progression, unacceptable toxicity or withdrawal of consent. The median patient age was 57 years, 60% of patients were male and 40% had an elevated serum lactate dehydrogenase level. The median time from first diagnosis to diagnosis of advanced melanoma was 1.7 years.

3.3 The primary outcome of the CA184-024 trial was overall survival: median overall survival differed by 2.1 months, from 9.1 months with dacarbazine alone to 11.2 months with ipilimumab 10 mg/kg plus dacarbazine, and there was a 5.7 month survival gain over the 5 year trial. The hazard ratio for death was 0.72 (95% confidence interval [CI] 0.59 to 0.87; p<0.001). There was no statistically significant difference in the median progression-free survival between ipilimumab 10 mg/kg plus dacarbazine and dacarbazine alone (2.8 compared with 2.6 months), but ipilimumab 10 mg/kg statistically significantly increased progression-free survival compared with dacarbazine, with a hazard ratio for progression of 0.76 (95% CI 0.63 to 0.93; p=0.0064). The response rate was statistically significantly improved with ipilimumab 10 mg/kg plus dacarbazine compared with dacarbazine alone (15.2% compared with 10.3%; p=0.03) and the duration of response was statistically significantly longer (median 19.3 compared with 8.1 months; p=0.03) in the ipilimumab group. There were no statistically significant differences in disease control rate (which included response and stable disease rates), time to response, or European Organisation for Research and Treatment of Cancer

questionnaire (EORTC-QLQ-C30) functioning scales or symptom scales between treatment arms.

3.4 Long-term safety data were available from the CA184-024 trial, which indicated that the safety profile of ipilimumab was maintained throughout therapy. Severe, serious, drug-related and adverse events leading to drug discontinuation were all more frequent in the ipilimumab 10 mg/kg plus dacarbazine group (46%) than in the group treated with dacarbazine alone (18%). Discontinuations because of trial-drug toxicity led to 37% of patients not receiving all 4 doses of ipilimumab 10 mg/kg. Of the patients receiving ipilimumab, 77.7% experienced an immune-related adverse event (41.7% were grade 3 or 4 events). The most commonly reported adverse events were hepatic-related with 17.4% to 20.7% of patients experiencing grade 3 or 4 elevations in liver function values, but these reactions were generally reversible. Other adverse events observed in the trial were dermatological events, gastrointestinal events, pyrexia, chills and weight loss. The safety profile of ipilimumab was similar in patients during the induction period and in patients having treatment for longer than 2 years.

3.5 The MDX010-08 trial was a multicentre, randomised, open-label trial carried out in the USA, including adults with advanced (unresectable or metastatic) melanoma who had not received prior chemotherapy and had a life expectancy of over 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 alone (n=40). The trial was randomised using a central randomisation scheme with stratification by random block size, and because it was carried out in the USA it did not contain any UK patients. The trial was also not designed to detect differences in survival between the 2 treatment arms. The manufacturer provided details of pre-specified subgroups of patients within the trials including median age (60 years and 66 years for the ipilimumab plus

dacarbazine and ipilimumab groups respectively), sex (74.3% and 56.8% male for the ipilimumab plus dacarbazine and ipilimumab groups respectively), stage of metastasis, time since diagnosis and lactate dehydrogenase level.

3.6 The MDX010-08 trial demonstrated that no statistically significant difference was observed for the primary outcome of objective response rate between ipilimumab alone and ipilimumab plus dacarbazine. There was also no statistically significant difference in overall survival between the ipilimumab 3 mg/kg plus dacarbazine group and the ipilimumab alone group. The results appeared to favour ipilimumab plus dacarbazine over ipilimumab alone (median overall survival of 14.3 months compared with 11.4 months with a hazard ratio for overall survival of 0.75 [95% CI 0.45 to 1.24] and a 1-year overall survival rate of 62% compared with 45%), but the trial was underpowered to detect statistically significant differences in overall survival. All patients in both treatment groups experienced at least 1 adverse event, with 65.7% in the ipilimumab plus dacarbazine group compared with 53.8% in the ipilimumab alone group experiencing 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 group. One person died from a suspected drug-related adverse event in the ipilimumab plus dacarbazine group and 2 people died in the ipilimumab alone group.

3.7 The BRIM-3 trial was a multinational, randomised, crossover trial including adults with previously untreated advanced (unresectable or metastatic) melanoma that was also BRAF V600 mutation-positive, and who had a life expectancy of over 3 months. People received either vemurafenib 960 mg (n=337) twice daily or dacarbazine 1000 mg/m^2 (n=338) every 3 weeks. Randomisation was used to assign patients in a 1:1 ratio. The manufacturer included details of sub-populations within the trial. These

included the age (median 56 years in the vemurafenib group and 52 years in the dacarbazine group) and sex of patients (59.4% and 53.6% male respectively), their Eastern Cooperative Oncology Group (ECOG) performance status (most patients in both groups had a score of 0), their stage of metastasis (most patients in both groups had metastases at the M1c stage; distant metastases were found) and lactate dehydrogenase level (most patients in both groups had levels above the upper limit of normal).

3.8 The BRIM-3 trial demonstrated that vemurafenib statistically significantly increased overall survival in patients who had BRAF V600 mutation-positive melanoma when compared with dacarbazine. Median overall survival was increased by 3.6 months in the vemurafenib group (13.2 months compared with 9.6 months; hazard ratio 0.62; 95% CI 0.49 to 0.77; p<0.001). Overall survival rates were higher with vemurafenib than dacarbazine at 6 months (84% compared with 64%). Progression-free survival was also statistically significantly increased for patients in the vemurafenib treatment group, with a median progression-free survival of 5.3 months compared with 1.6 months and a hazard ratio for progression of 0.26 (95% CI 0.20 to 0.33; p<0.001). The response rate was statistically significantly improved with vemurafenib compared with dacarbazine (48.4% compared with 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. The BRIM-3 trial used the Functional Assessment of Cancer Therapy Melanoma (FACT-M) questionnaire to measure health-related quality of life but the data were not reported because of low completion rates.

3.9 The manufacturer also presented the BREAK-3 trial that compared dabrafenib 150 mg with dacarbazine 1000 mg/m^2 in adults with advanced (unresectable or metastatic) melanoma who tested positive for the BRAF V600 mutation. The manufacturer included this trial as part of the

mixed treatment comparison described in section 3.15 but did not include it in the cost-effectiveness analyses because it was not included in the NICE scope, had limited publicly available data, and dabrafenib did not have a UK price.

3.10 Two ongoing US retrospective, observational studies (CA184-332 [n=61] and CA184-338 [n=120]) for ipilimumab 3 mg/kg in people who had not previously received treatment were also included in the manufacturer's submission. The median overall survival for ipilimumab 3 mg/kg monotherapy was 11.5 months in the CA184-332 trial and 14.3 months in the CA184-338 trial. The manufacturer reported that in the CA184-338 trial, 54.2% of people treated with ipilimumab 3 mg/kg experienced a drug-related adverse event. BRAF V600 mutation status data were available, and the manufacturer suggested that a post-hoc analysis of CA184-338 supported 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 observed between patients who have BRAF V600 mutation-positive melanoma and those who have BRAF V600 mutation-negative melanoma.

3.11 The manufacturer presented a pooled analysis of patients (n=78) randomised to 3 mg/kg ipilimumab monotherapy (MDX010-08, CA184-004, CA184-022 and MDX010-020). It was noted that 43 out of 78 patients had received prior immunotherapy. The manufacturer stated that CA184-004 and CA184-022 were not included as stand-alone trials because the patient numbers were too small but stated that they demonstrated the clinical equivalence between 3 mg/kg and 10 mg/kg doses of ipilimumab and supported the extrapolation of the CA184-024 data. The MDX010-020 trial was a double-blind trial including patients with advanced (unresectable or metastatic) melanoma who had previously been treated with regimens containing 1 or more of the following: interleukin-2, dacarbazine, temozolomide or other chemotherapies.

Patients were randomised into 3 groups (in a ratio of 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 was up to 55 months. The hazard ratio for comparison of overall survival between 3 mg/kg ipilimumab alone and gp100 was 0.66 (95% CI 0.51 to 0.87; p=0.0026). The median overall survival for ipilimumab 3 mg/kg monotherapy in this pooled analysis was 13.5 months (95% CI 11.2 to 19.6).

3.12 The manufacturer made several assumptions to support the clinical and cost effectiveness of 3 mg/kg ipilimumab monotherapy. The first key assumption was that ipilimumab 3 mg/kg and 10 mg/kg were clinically equivalent. Data from 2 trials (CA184-004, 36 chemotherapy-naive patients and CA184-022, 18 chemotherapy-naive patients) comparing ipilimumab 3 mg/kg and 10 mg/kg were presented in support of this assumption. The manufacturer highlighted that the trials indicated that the survival associated with ipilimumab 3 mg/kg and 10 mg/kg was similar, with median overall survival of 14.3 and 11.2 months respectively. The manufacturer also provided pooled data comparing overall survival profiles of ipilimumab 3 mg/kg (MDX010-020 and CA184-022) and 10 mg/kg (CA184-007, CA184-008 and CA184-022) for a mixed population. The manufacturer stated that no statistically significant difference in survival was observed between the 3 mg/kg and 10 mg/kg treatment arms across the whole population. The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has requested that the manufacturer conduct a study on any relevant difference in efficacy between 3 mg/kg and 10 mg/kg.

3.13 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 in

which 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. 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. The CHMP concluded that ipilimumab pharmacokinetic data were not significantly affected by concomitant dacarbazine.

3.14 The manufacturer provided information to demonstrate that ipilimumab efficacy is similar in patients with previously untreated and previously treated melanoma. The manufacturer stated that the results of the MDX010-020 (previously treated melanoma) and CA184-024 trials (previously untreated melanoma) 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 CHMP accepted this evidence from the MDX010-020 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 adults with previously treated advanced (unresectable or metastatic) melanoma. The CHMP commented in the licensing 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 patients with previously treated melanoma and the baseline characteristics of the patients included in the pivotal studies in previously treated and previously untreated subpopulations were similar.

- Ipilimumab pharmacokinetic data were not substantially affected by concomitant dacarbazine.
- There is no biological rationale to suspect a different activity for ipilimumab treatment in the first- or next-line setting.

The CHMP also requested that the manufacturer conduct a study on any relevant difference in efficacy between 3 mg/kg and 10 mg/kg.

3.15 Data from 3 (CA184-024, BREAK-3 and BRIM-3) of the 4 randomised controlled trials identified were analysed as a mixed treatment comparison to provide a comparison between ipilimumab 10 mg/kg and BRAF inhibitors. The manufacturer stated that given that ipilimumab 3 mg/kg and ipilimumab 10 mg/kg could be considered equivalent, 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. The manufacturer constructed a forest plot of overall survival which demonstrated that although ipilimumab plus dacarbazine was associated with a statistically significant improvement in survival compared with dacarbazine alone (hazard ratio [HR] 0.72; 95% CI 0.55 to 0.95), there were no statistically significant differences for ipilimumab plus dacarbazine compared with vemurafenib (HR 1.16) or dabrafenib (HR 1.19). Indirect comparisons using the Bucher equation showed that there was no statistically significant difference in efficacy for ipilimumab plus dacarbazine compared with vemurafenib (HR 1.16; 95% CI 0.86 to 1.56) and dabrafenib (HR 1.18; 95% CI 0.48 to 2.93). The manufacturer commented that the main difference in patients enrolled in the clinical trials was their BRAF V600 mutation status and previous treatment.

3.16 The manufacturer conducted a de novo analysis to estimate the cost effectiveness of ipilimumab compared with dacarbazine in patients who

have BRAF V600 mutation-negative melanoma, and of ipilimumab compared with dacarbazine and vemurafenib in patients who have BRAF V600 mutation-positive melanoma. The manufacturer developed a semi-Markov partitioned survival model with health states used to represent tiers of treatment, incorporating second-line active treatment and third-line best supportive care. 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 before death). The model assumes 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.

3.17 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. Patients' health-related quality of life was estimated from time to death as an intermediate outcome because the manufacturer determined that disease progression was the most meaningful way of estimating health-related quality of life. The proportion of patients receiving each of the 4 doses needed 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 MDX010-020 clinical trial.

3.18 To add to the manufacturer's previous assumptions about dose equivalence and that ipilimumab plus dacarbazine and ipilimumab alone were equally effective, the manufacturer also assumed that the efficacy of ipilimumab in patients with and without the BRAF V600 mutation 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-naive dataset analysis (CA184-004, MDX010-08, CA184-022 and MDX010-020), stating that overall and progression-free survival outcomes were similar using the 2 datasets. For vemurafenib, the manufacturer stated that there was no difference between the dacarbazine arms of the CA184-024 and BRIM-3 trials and therefore data from the vemurafenib arm of the BRIM-3 trial were incorporated directly into the model.

3.19 The transition to second- and third-line treatment was modelled based on progression-free survival data, whereas overall survival data were used to model transition to death. For first-line treatment with ipilimumab or dacarbazine, a 3-part curve fit for overall survival was used based on data from CA184-024 and for vemurafenib a 5-part curve fit was used based on data from the BRIM-3 trial. For second-line treatments, overall survival was based on first-line survival curves but adjusted downwards to account for poorer outcomes on second-line treatment 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 treatment. The manufacturer highlighted that for patients treated with ipilimumab, using progression-free survival overestimates the number of patients moving to second-line treatment because ipilimumab's mode of action means it is

possible for a patient's condition to initially progress and then become stable or respond to treatment. This may overestimate the cost in the ipilimumab arm because costs of first-line treatment with ipilimumab are almost static, whereas the costs of second-line treatment depend on the duration of treatment.

3.20 The same ipilimumab patient access scheme will be in place as agreed in Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (NICE technology appraisal guidance 268; hereafter referred to as TA268). The cost of vemurafenib was presumed to be 4 packs of tablets every 4 cycles as in Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (NICE technology appraisal guidance 269) and included the agreed patient access scheme. 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 the 2 drugs were taken from the specific product characteristics. Second-line costs for ipilimumab were also taken from the previous NICE appraisal, TA268. 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.

3.21 For patients who have BRAF V600 mutation-positive melanoma, base-case results indicated that vemurafenib was dominated by (that is, was more expensive and less effective than) ipilimumab because it was associated with higher costs and fewer quality-adjusted life years (QALYs). A comparison of ipilimumab with dacarbazine resulted in an incremental cost-effectiveness ratio (ICER) of £31,559 per QALY gained using the CA184-024 results and £28,465 per QALY gained when using the pooled chemotherapy-naive data for ipilimumab. For patients who have BRAF V600 mutation-negative melanoma, the ICER for ipilimumab

compared with dacarbazine was £16,958 per QALY gained using the CA184-024 trial results and £17,866 per QALY gained using the pooled chemotherapy-naive data.

3.22 The manufacturer conducted a 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. 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. 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. Data from the CA184-024 trial were used to calculate ICERs for ipilimumab compared with vemurafenib and dacarbazine. Ipilimumab dominated (that is, was less expensive and more effective than) vemurafenib and the ICER was £31,619 per QALY gained compared with dacarbazine. The manufacturer used 2 different maximum acceptable ICERs to calculate the incremental net benefit: £30,000 per QALY gained when comparing with vemurafenib and £50,000 per QALY gained when comparing with dacarbazine. The manufacturer stated, after carrying out probabilistic sensitivity analysis, that the probability of ipilimumab being cost effective when compared with dacarbazine was 96%, using £50,000 per QALY gained as the maximum acceptable ICER. There was a 40% probability of ipilimumab being cost effective if the maximum acceptable ICER was £30,000 per QALY gained. The manufacturer suggested an ICER for ipilimumab compared with dacarbazine of £49,579 per QALY gained as the most pessimistic outcome, assuming a single parameter curve fit using a log-normal distribution for overall survival, but it emphasised that single parametric curve fits were a poor fit to the data.

3.23 The ERG stated that the manufacturer had identified all relevant randomised controlled trials and that adequate trial details were 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 treatment) compared with dacarbazine, vemurafenib or dabrafenib for treating previously untreated advanced (unresectable or metastatic) 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 underpowered to detect a statistically significant difference in overall survival. The ERG stated that the pooled analysis of chemotherapy-naive patients could result in double counting because 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 trials and the pooled analysis and, additionally, it was inappropriate to compare the results of these trials with the dacarbazine-alone arm of the CA184-024 trial because of differences in trial design and patient characteristics.

3.24 The ERG stated that the manufacturer's assumption that 3 mg/kg and 10 mg/kg doses of ipilimumab have equivalent clinical effectiveness was not appropriate. The ERG highlighted that survival was better with ipilimumab 10 mg/kg than 3 mg/kg in the CA184-022 trial (n=18; chemotherapy treatment-naive patients), though this improvement was not statistically significant (HR 0.875; 95% CI 0.593 to 1.291) and the overall response rate was statistically significantly improved with ipilimumab 10 mg/kg, whereas grade 3 or 4 adverse events were more common at the higher dose. The ERG noted that although the CA184-004 trial indicated no meaningful differences with different doses of ipilimumab, the numbers in this trial were very small (n=36; chemotherapy treatment-naive patients). In response to clarification, the manufacturer

presented results of a pooled analysis that compared overall survival profiles for ipilimumab 3 mg/kg from the MDX010-020 and CA184-022 trials and 10 mg/kg from the CA184-007, CA184-008 and CA184-022 trials for a mixed population of patients with previously treated or untreated melanoma. The ERG stated that the results of this pooled analysis suggested that a 10 mg/kg dose could be better than a 3 mg/kg dose in terms of overall survival but that methods for pooling had not been presented and it was unable to confirm the reliability of this analysis. The ERG also noted that this analysis included primarily previously treated patients. The ERG stated that the US Food and Drug Administration and the European Medicines Agency both commented on the 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.

3.25 The ERG also stated that the manufacturer's assumption that ipilimumab alone and ipilimumab plus dacarbazine have equivalent clinical effectiveness was not appropriate. 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 overall survival 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.

3.26 The ERG stated that it did not consider the indirect comparisons and mixed treatment comparisons conducted by the manufacturer to be appropriate because of different patient characteristics and BRAF status. The ERG also noted the difference in trial designs and that the difference in the mechanism of action between ipilimumab and the BRAF inhibitors resulted 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 these concerns, the ERG stated that the survival benefit associated with ipilimumab 3 mg/kg was likely to be overestimated in the manufacturer's submission.

3.27 The ERG expressed some major concerns about the assumptions in the manufacturer's model, particularly about the relative efficacy data used in the model because of the clinical assumptions necessary (see sections 3.12 and 3.13). 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 raised concerns about the exchangeability of populations across the trials. In addition, the ERG stated that using the mixed treatment comparison to check consistency of results indicated that using the independent arm from the BRIM-3 trial directly favoured ipilimumab.

3.28 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, resulting in oversimplified assumptions. 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 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, TA268. The ERG acknowledged the manufacturer's clarification that this would have been difficult to implement in the cohort model structure because patients progressed to second-line treatment at different time points, but emphasised that if treatment sequencing was included, the additional complexity to model sequencing should be incorporated. When observing the manufacturer's

scenario analysis, the ERG considered the 'no active second-line treatments' to be the most important because 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 per QALY gained and when comparing with vemurafenib, the ICER became £28,980 per QALY gained in the BRAF V600 mutation-positive population.

3.29 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 assumption used in the model was that they continue to follow the ipilimumab overall survival curve from the CA184-024 trial until they die, indicating a sustained overall survival benefit for first-line ipilimumab. 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 (HR 1.21). Once patients move onto best supportive care, the assumption used in the model was that the patients followed the overall survival curve of first-line dacarbazine. The ERG stated that the manufacturer had not supplied any evidence for the assumption that patients receiving first-line ipilimumab maintained sustained benefit of overall survival in the long term whereas patients receiving ipilimumab second-line did not. The ERG commented that this approach favoured ipilimumab.

3.30 The ERG stated that the modelled treatment pathways for patients who have BRAF V600 mutation-positive melanoma demonstrated similar

inconsistencies in the use of overall survival curves. When ipilimumab was provided to patients as first-line treatment, the overall survival curve from the CA184-024 trial was used in the modelling. 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.

3.31 The ERG had concerns that no direct EQ-5D data were collected and that the Rowen algorithm may not be sufficiently generalisable to the current appraisal population. 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 effects.

3.32 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, if it was assumed that patients remain on the same overall survival curve of second-line treatment, the ICER for ipilimumab compared with dacarbazine increased from £16,958 to £18,833 per QALY gained. The ERG also carried out analyses using the overall survival curve of ipilimumab second line for best supportive care and the overall survival curve of dacarbazine first-line for best supportive care, resulting in an increase in the ICER to £40,005 per QALY gained and £56,486 per QALY gained respectively. In the BRAF V600 mutation-positive population, 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. 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.

3.33 The ERG noted that it was possible 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. The ERG therefore turned off the sequential use of treatments in the manufacturer's model so that it followed a conventional 3-state cancer model with the only additional line of treatment being that of best supportive care. This followed the more conventional 3-state cancer model. The ERG also presented an analysis assuming the same overall survival curves for patients who progress to best supportive care that 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, when assuming that patients did not receive any second-line treatment, the ICER was £28,980 per QALY gained.

3.34 The ERG further explored the manufacturer's assumption that ipilimumab 3 mg/kg was clinically equivalent to ipilimumab 10 mg/kg, using the pooled overall survival data provided by the manufacturer in response to clarification. The ERG estimated the implied hazard ratio for 3 mg/kg relative to 10 mg/kg by extracting data from the Kaplan–Meier curves for both doses. 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 was no longer less costly and more effective as in the manufacturer's base-case analysis, but instead became less costly and less effective with a resulting ICER of £56,958 per QALY gained for vemurafenib compared with ipilimumab.

3.35 The ERG did not believe there was conclusive evidence to suggest that ipilimumab plus dacarbazine was equivalent to ipilimumab alone. The ERG found that the ICER for ipilimumab compared with dacarbazine increased from £16,958 to £73,615 per QALY gained in the BRAF V600 mutation-negative population when using a hazard ratio of 0.75 from the MDX010-08 trial. 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.

3.36 The ERG noticed a discrepancy in the cost per weekly cycle of ipilimumab depending on whether treatment was first-line (£1055) or second-line (£1499). When the ERG explored this price difference by incorporating second-line costs, the ICER for ipilimumab compared with dacarbazine increased from £16,958 to £25,720 per QALY gained in the BRAF V600 mutation-negative population. Ipilimumab still dominated vemurafenib in the BRAF V600 mutation-positive population. The ERG also compared the estimates of cost effectiveness with those based on utility values for pre- and post-progression as used in the previous ipilimumab appraisal, TA268. When the ERG used these utility values, the ICER increased from £16,958 to £19,320 per QALY gained for the comparison of ipilimumab with dacarbazine in the BRAF V600 mutation-negative population.

3.37 The ERG presented additional analyses exploring the cost effectiveness of ipilimumab 3 mg/kg monotherapy, based on a conventional 3-state

model that observed 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 because the adjustment produced lower QALYs for ipilimumab (reduced from 2.35 to 1.56 mean QALYs). 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 (reduction in QALYs from 2.35 to 1.50 for ipilimumab). When the ERG compared ipilimumab with vemurafenib, vemurafenib dominated ipilimumab in both scenarios.

Manufacturer's response to consultation

3.38 In response to consultation, the manufacturer presented updated analyses using data from the MDX010-20 and BRIM-3 trials. The manufacturer adjusted the overall survival curve for previously treated patients receiving 3 mg/kg ipilimumab in the MDX010-20 trial to predict overall survival for previously untreated patients receiving 3 mg/kg ipilimumab. The manufacturer used ipilimumab overall survival and progression-free survival data from the MDX010-20 trial and overall survival and progression-free survival data for dacarbazine from the CA184-024 trial. The baseline characteristics of patients in the 2 trials were similar, although patients in the MDX010-20 trial generally had greater tumour burden. Therefore the manufacturer used a Cox proportional hazards model fitted to data from the 3 mg/kg ipilimumab arm of the MDX010-20 trial to predict overall survival for a group of patients with the baseline characteristics of those in the CA184-024 trial.

3.39 Five prognostic factors – gender, ECOG performance status, visceral disease status, brain metastases and lactate dehydrogenase levels – were modelled to produce an average survival curve using weightings from the CA184-024 trial. The resulting overall survival curve represented predicted overall survival for the 3 mg/kg ipilimumab dose in the first-line

setting. The updated overall survival Kaplan–Meier data were applied directly into the model and the curve extrapolated based on evidence from the CA184-024 trial. In the updated base-case analysis, the manufacturer used the adjusted overall survival data for the first 4.5 years and then used the overall survival curve from the CA184-024 trial. The manufacturer considered this appropriate because the proportion of patients alive at 4.5 years was equal to that for the adjusted overall survival data. The manufacturer incorporated the adjusted overall survival data directly into its updated model for the base-case analysis. The higher number of doses received by patients in the MDX010-20 trial was also incorporated in the base-case analysis. No adjustment was carried out for the progression-free survival curve because it was considered unnecessary.

3.40 In the manufacturer's original submission, it assumed that there was no difference in the overall survival for patients between the dacarbazine control arms of the CA184-024 and BRIM-3 trials. The manufacturer reported in its response to consultation that the latest follow-up data from the BRIM-3 trial show differences in the overall survival curves for the 2 dacarbazine patient populations. A proportion of patients (more than 20%) in the BRIM-3 trial received ipilimumab after vemurafenib or dacarbazine, so survival for vemurafenib was potentially overestimated. The manufacturer updated the vemurafenib overall survival curve from the BRIM-3 trial to remove the effect of patients who received ipilimumab second-line. No adjustments had to be made for patients in the MDX010-20 and CA184-024 trials because patients were not allowed to cross over from the dacarbazine group to the ipilimumab group, and no patients received vemurafenib after ipilimumab or dacarbazine. The overall survival curve for vemurafenib was also further adjusted to account for different patient baseline characteristics in the BRIM-3 and CA184-024 trials.

3.41 The manufacturer presented updated ICERs using the 3-state model and adjusted overall survival curves. In the base case, the manufacturer calculated an ICER of £47,899 per QALY gained for ipilimumab compared with dacarbazine and an ICER of £28,642 per QALY gained for ipilimumab compared with vemurafenib. The manufacturer considered that the ICER presented for ipilimumab compared with vemurafenib may be a conservative estimate because the benefits of vemurafenib over dacarbazine looked unrealistically high, in light of further data from the BRIM-3 trial. The manufacturer addressed this in its scenario analysis (by assuming that the proportion of patients alive in the vemurafenib group was equal to dacarbazine at and after 30 months from the start of the trial) and the ICER for ipilimumab compared with vemurafenib was reduced to £12,967 per QALY gained.

3.42 The manufacturer also carried out 2 modifications to the sequential model to enhance its validity. Firstly, the mortality hazard for third-line treatment was assumed to be the same as for second-line ipilimumab. The second modification involved the use of survival curves from the MDX010-20 trial rather than the use of hazard ratios to estimate efficacy of second-line ipilimumab. Using the sequential model decreased the ICER for ipilimumab compared with dacarbazine from £47,899 per QALY gained to £41,016 per QALY gained. The manufacturer also indicated that ipilimumab may be used by clinicians to treat patients who have BRAF V600 mutation-positive melanoma if they had favourable prognostic characteristics but only observational studies were available to support this assumption. The lack of data meant that the manufacturer did not present a sequential comparison of ipilimumab and vemurafenib.

3.43 The manufacturer also calculated a ‘worst-case scenario’ ICER for the treatment of patients who have previously untreated melanoma using unadjusted data from the MDX010-20 trial. For the ICER calculation, the overall survival and progression-free survival were taken from the model

submitted in the previous appraisal, TA268. The efficacy outcomes for dacarbazine were from the CA184-024 trial and for vemurafenib were from the BRIM-3 trial because these are likely to overestimate the efficacy of the treatments compared with ipilimumab. The ICER for ipilimumab compared with dacarbazine was £58,593 per QALY gained and vemurafenib dominated ipilimumab. The manufacturer also applied an adjustment of the MDX010-20 overall survival curve as a hazard ratio and this produced an ICER of £37,575 per QALY gained for ipilimumab compared with dacarbazine and £15,592 per QALY gained for ipilimumab compared with vemurafenib. The manufacturer also provided an analysis to demonstrate that the proportion of patients alive with vemurafenib and dacarbazine at 30 months was equal. This scenario analysis produced an ICER of £12,967 per QALY gained when comparing ipilimumab and vemurafenib.

Evidence Review Group's response to manufacturer's consultation comments

3.44 The ERG questioned the prognostic factors used by the manufacturer to adjust the overall survival curve from the MDX010-20 trial to reflect previously untreated melanoma. The ERG noted that baseline disease stage was excluded from the model despite differences between trials and, although the ERG agreed with the use of a Cox proportional model, it could not verify the overall survival curve for ipilimumab or vemurafenib because the ERG did not have the individual patient-level data to fit the model. The ERG also had reservations about the use of this corrected curve in the model, with the adjusted overall survival curve directly modelled for the first 4.5 years and then an extrapolation being used beyond this point, because this was not consistent with the previous appraisal, TA268. The ERG was also unsure why a cut-off of 4.5 years was used and would have preferred the manufacturer to explore alternative curve fits and explain whether adjustment for censoring had been carried out. There was also concern about the uncertainty in the overall survival curve beyond 3 years because, in the MDX010-20 trial,

only 37 patients were still at risk at the 3-year point. The ERG would have preferred to see the use of parametric tools in developing the adjustments and analysis that did not break randomisation when comparing the comparator treatment arms.

3.45 The ERG considered the manufacturer's use of a 3-state model and survival curves from the MDX010-20 trial directly in the model to be appropriate. No details were provided of how the manufacturer had implemented the curves within the model and therefore the approach could not be verified by the ERG. There was also concern about the switching of overall survival curves between lines of treatment. The ERG noted that the manufacturer had partly addressed this issue by assuming that the hazard mortality for best supportive care was the same as second-line ipilimumab rather than first-line, as in the manufacturer's original submission. The ERG commented that the manufacturer's approach only addressed the observed differences between trial populations and did not control for unobservable differences between patients.

3.46 Full details of all the evidence are in the manufacturer's original submission, the manufacturer's response to consultation, the ERG report and the ERG's critique of the manufacturer's response to consultation.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ipilimumab, having considered evidence on the nature of advanced (unresectable or metastatic) melanoma and the value placed on the benefits of ipilimumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.1 The Committee considered the nature of the condition and current clinical practice for treating patients with previously untreated advanced (unresectable or metastatic) melanoma. The Committee was aware that unresectable or metastatic melanoma substantially worsens quality of life and is a life-limiting incurable condition. Without effective new therapies, the prognosis for advanced disease is very poor. The Committee heard from the clinical specialists that for patients who have BRAF V600 mutation-negative melanoma, dacarbazine is the only first-line treatment option currently available and it has never been shown to have survival benefit. The Committee also noted comments received during consultation from patient organisations, healthcare professionals and carers that dacarbazine had not been shown to have a survival benefit. The clinical specialists stated that consequently, current practice included administering dacarbazine, usually with early scanning after 1 to 3 courses, before moving to second-line ipilimumab. For patients who have BRAF V600 mutation-positive melanoma, the Committee heard that vemurafenib was likely to remain the standard first-line treatment option especially in those with a high disease burden, but understood that ipilimumab would be valuable as a first-line option in approximately 20–30% of patients with small-volume indolent disease for whom vemurafenib could be reserved as rescue treatment later in the pathway. The clinical specialists stated that although it is not possible to identify patients most likely to experience a response with ipilimumab, in some patients whose condition responds to treatment it was associated with a very durable response. Patient experts at the first committee meeting emphasised that having the choice of ipilimumab as a first-line treatment would be valued by patients and their families and a treatment that prolongs survival could allow people to return to normal life. The Committee concluded that there was an unmet need for effective therapies in this patient population.

4.2 The Committee discussed the clinical evidence presented in the manufacturer's original submission for ipilimumab alone compared with

dacarbazine as a first-line treatment. The Committee noted that the pivotal trial in this submission, CA184-024, assessed ipilimumab 10 mg/kg plus dacarbazine, whereas the licensed regimen was 4 doses of ipilimumab 3 mg/kg alone over 12 weeks. The Committee was aware that in using data from this trial to estimate clinical effectiveness, the manufacturer had assumed that ipilimumab 3 mg/kg and 10 mg/kg were equivalent and that ipilimumab plus dacarbazine was equivalent to ipilimumab alone. The Committee was aware of the European Medicines Agency (EMA) considerations when extending the marketing authorisation for ipilimumab 3 mg/kg into the first-line setting (see section 3.14). The Committee understood that in estimating the benefit–risk balance, the EMA concluded that sufficient evidence of the efficacy of ipilimumab 3 mg/kg in previously untreated patients had been provided. It also understood that this conclusion was partly based on having already established the efficacy of 3 mg/kg ipilimumab monotherapy in previously treated melanoma, taking into account the similarity of the previously treated and previously untreated sub-populations in the clinical studies. The Committee noted that during consultation, the manufacturer had accepted the Committee's reluctance to agree to equivalent efficacy of 10 mg/kg ipilimumab plus dacarbazine and 3 mg/kg ipilimumab alone. The manufacturer therefore proposed an alternative approach to assessing the clinical and cost effectiveness of 3 mg/kg ipilimumab monotherapy first-line. This method used data from the MDX010-20 trial, which had been the pivotal trial for Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (NICE technology appraisal guidance 268; hereafter referred to as TA268). The Committee concluded that this provided additional relevant evidence and expressed disappointment that the manufacturer had not used the information from the full MDX010-20 trial in its original submission.

4.3 The Committee further considered these data, which compared 3 mg/kg ipilimumab alone, 3 mg/kg ipilimumab plus gp100 and gp100 alone in the

second-line setting. The Committee agreed that the Kaplan–Meier overall survival curves from CA184-024 and MDX010-20 were similar, with both demonstrating an approximate 10% long-term overall survival benefit and no treatment crossover, and noted that combination treatment was used in both trials. The Committee also noted that the trials had different doses of ipilimumab, first-line compared with second-line trial populations, and different comparators. The Committee heard from the clinical specialists that treatments would usually be more effective rather than less effective if used earlier in therapy, and that there was no biologically plausible reason for ipilimumab monotherapy at a dose of 3 mg/kg to be less effective when used first-line rather than second-line. The Committee acknowledged that the shape of the Kaplan–Meier curves was similar in the first- and second-line settings and both indicated that approximately 10% of patients experienced a sustained overall survival benefit lasting until the end of the 5-year trials. The Committee concluded that it is plausible that 3 mg/kg ipilimumab could give the same treatment effect in both untreated and previously treated melanoma and that the use of the MDX010-20 trial data from the previous appraisal (TA268) provided more plausible estimates of the clinical effectiveness of 3 mg/kg ipilimumab in the first-line setting than those provided in the manufacturer's original submission.

4.4 The Committee discussed the overall survival results from the clinical trials and noted that the difference in median overall survival was 2.1 months when given first-line at 10 mg/kg in combination with dacarbazine, and 3.7 months when given alone at 3 mg/kg as a second-line treatment. The Committee noted that, because of the long duration and lack of crossover in the CA184-024 trial, patient-level data on mean overall survival were also available, which included all patients in the trial up to 5 years. This demonstrated a mean overall survival gain of 5.7 months for patients in the ipilimumab arm. The Committee concluded

that both trials had demonstrated an overall survival gain for patients treated with ipilimumab, and that this gain was at least 3 months.

4.5 The Committee discussed the evidence available for ipilimumab 3 mg/kg alone compared with vemurafenib in the BRAF V600 mutation-positive population. The Committee was aware that no data were available for a direct comparison and the manufacturer had attempted to conduct an indirect comparison using the CA184-024 and BRIM-3 trials in its original submission. In addition to its previous observations on the 10 mg/kg dose of ipilimumab in the CA184-024 trial, the Committee had expressed concern that patients in the vemurafenib BRIM-3 trial may have had a worse prognosis than those in the ipilimumab trial, which would affect the calculation of differential effectiveness. In its updated analysis in response to consultation, the manufacturer had made an adjustment to take account of the worse prognosis of patients in BRIM-3, and also the degree of subsequent ipilimumab therapy. Following the various adjustments, the Committee concluded that the data were suitable for estimating the clinical effectiveness of ipilimumab 3 mg/kg compared with vemurafenib.

4.6 The Committee discussed comments received during consultation about patients with ocular melanoma who might be excluded from the preliminary 'only in the context of research' recommendation because they are usually excluded from clinical trials. The Committee heard from the clinical specialists that, even though ocular melanoma is biologically different from cutaneous melanoma, patients are offered the same treatment options. The Committee concluded that patients with ocular melanoma could be included in the final guidance.

4.7 The Committee discussed the incremental cost-effectiveness ratios (ICERs) presented in the manufacturer's original model, focusing in particular on the extent of the impact of the manufacturer's assumptions on the results. The Committee noted that the Evidence Review Group (ERG) had performed exploratory analyses that were intended to better

reflect the clinical effectiveness of ipilimumab 3 mg/kg alone in the model, as well as adjusting a parameter in the overall survival data for concomitant dacarbazine. The Committee noted that this resulted in ICERs ranging from approximately £60,000 to £74,000 per quality-adjusted life year (QALY) gained for ipilimumab compared with dacarbazine in the BRAF V600 mutation-negative population and in ipilimumab being less costly and less effective compared with vemurafenib in the BRAF V600 mutation-positive population. The Committee noted that there was a difference in the cost of ipilimumab between first- and second-line use in the manufacturer's model. The manufacturer explained that the costs were based on trial data and that the number of patients who received the fourth ipilimumab 10 mg/kg dose first-line in the CA184-024 trial was smaller than the number who received the fourth ipilimumab 3 mg/kg dose second-line in the MDX010-020 trial. The Committee discussed whether this was because of greater adverse events associated with the higher dose of ipilimumab, but the manufacturer stated that the higher efficacy of ipilimumab would also need to be taken into account. The Committee considered that this suggestion of increased effectiveness with more doses was not in line with the manufacturer's assumption that ipilimumab 10 mg/kg was clinically equivalent to ipilimumab 3 mg/kg. It also noted that the ERG's analyses, which explored the impact of assuming that first-line costs also apply in second-line treatment, resulted in an increase in the ICER for ipilimumab compared with dacarbazine from approximately £17,000 to £25,700 per QALY gained in the BRAF V600 mutation-negative population.

4.8 The Committee considered the exploratory cost-effectiveness analysis presented by the ERG, based on the manufacturer's original model, which included modelling of only first-line use, and assumed a reduction in efficacy for a 3 mg/kg rather than a 10 mg/kg dose and a reduction in effectiveness in the absence of concomitant dacarbazine. The Committee

noted in the first committee meeting that this approach resulted in high ICERs compared with dacarbazine. It also resulted in ipilimumab being dominated by (that is, being more expensive and less effective than) vemurafenib. It also noted that these estimates included an estimate of QALYs gained approximately 10 to 20 times lower than the original base case for the comparison of ipilimumab with dacarbazine. The Committee considered that these estimated QALY gains were not plausible when taking into account the long-term survival shown in approximately 10% of patients in CA184-024 and the second-line trial MDX010-020 and did not consider this exploratory analysis further.

4.9 The Committee considered the manufacturer's response to consultation and the updated analyses using the adjusted overall survival curve from the second-line trial MDX010-20 to estimate the clinical effectiveness of 3 mg/kg ipilimumab first-line. The Committee was aware that in the updated base-case analysis, the manufacturer used overall survival and progression-free survival rates for ipilimumab from the previous appraisal (TA268), and overall survival and progression-free survival for dacarbazine were taken from the CA184-024 trial. Overall survival was then adjusted to take into account differences in the patient baseline characteristics. The Committee noted the ERG's concerns that the approach used by the manufacturer was inconsistent with the previous appraisal. The Committee heard from the manufacturer who clarified how the adjustments were applied. The Committee was satisfied that the adjustment and use of prognostic factors by the manufacturer in its updated analyses was appropriate.

4.10 The Committee considered the manufacturer's updated base-case results submitted in response to consultation (see section 3.39 onwards). It noted that the ICER for ipilimumab compared with dacarbazine was substantially higher than that in the original submission (£47,900 compared with £17,000 per QALY gained). It also noted that the ICER for ipilimumab

compared with vemurafenib was £28,600 per QALY gained, whereas in the original submission ipilimumab dominated vemurafenib. The Committee discussed the reasons for these differences and noted that the main reason was the use of a 3-state model, which had been preferred by the ERG, instead of the sequential modelling used in the manufacturer's original submission. The Committee also noted that the updated model incorporated a lower estimate of effectiveness for ipilimumab than that used in the original model, informed by the data from the MDX010-20 trial. The Committee agreed with the use of the 3-state model and accepted that there are some uncertainties about the assumption of equivalent effect of ipilimumab in previously untreated and treated melanoma. The Committee accepted that the updated ICER of £28,600 per QALY gained for ipilimumab compared with vemurafenib was plausible. It also accepted that the updated ICER of £47,900 per QALY gained for ipilimumab compared with dacarbazine was plausible, although it accepted that the ICER could be higher if other approaches were used to model overall survival.

4.11 The Committee discussed whether ipilimumab was innovative in its potential to make a significant and substantial impact on health-related benefits. The Committee heard from the clinical specialists and a patient representative (at the first meeting) that, after successful treatment, patients could lead an active and fulfilled life. The Committee acknowledged that few advances had been made in the treatment of advanced melanoma in recent years and that ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need.

4.12 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for

indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 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.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.13 The Committee discussed whether ipilimumab met the criteria set out for consideration as an end-of-life treatment. The Committee agreed that the life expectancy for people with advanced melanoma was less than 24 months. The Committee then discussed whether ipilimumab offered a 3-month survival gain. It agreed that there was sufficient evidence to indicate that the treatment offers an extension to life of at least an additional 3 months, compared with current NHS treatment (see section 4.4). The Committee heard from the clinical specialists that there are fewer than 1000 people in England with advanced melanoma who need first-line treatment, and this represents a small patient population. The Committee was satisfied that ipilimumab met the criteria for being a life-extending, end-of-life treatment and that the trial evidence presented for this was robust.

4.14 Having accepted that the supplementary advice for appraising a life-extending, end-of-life treatment applies, the Committee then considered the ICERs for ipilimumab compared with dacarbazine and compared with

vemurafenib. It accepted the manufacturer's ICER for ipilimumab compared with vemurafenib, which was £28,600 per QALY gained. It accepted that the ICER of £47,900 per QALY gained for ipilimumab compared with dacarbazine was plausible, while recognising that it could be higher if other approaches to modelling overall survival were used. The Committee concluded that, on balance, ipilimumab could be considered a cost-effective use of NHS resources for adults with previously untreated advanced (unresectable or metastatic) melanoma.

Summary of Appraisal Committee's key conclusions

TAXXX	**Appraisal title:**	**Section**
Key conclusion		
Ipilimumab is recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.		1.1
The Committee accepted that the updated ICER of £28,600 per QALY gained for ipilimumab compared with vemurafenib submitted by the manufacturer in response to consultation was plausible. It also accepted that the updated ICER, submitted in response to consultation, of £47,900 per QALY gained for ipilimumab compared with dacarbazine was plausible and in line with the previous appraisal (TA268), although it accepted that the ICER could be higher if other approaches are were used to model overall survival.		4.10
The Committee was satisfied that ipilimumab met the criteria for being a life-extending, end-of-life treatment and that the trial evidence presented for this was robust.		4.13
Current practice		
Clinical need of patients, including the availability of alternative treatments	Advanced melanoma can have a substantial negative impact on quality of life and, without effective new therapies, the prognosis for advanced disease is very poor.	4.1

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee understood that ipilimumab would be valuable as a first-line treatment option for people with advanced (unresectable or metastatic) malignant melanoma.	4.1
What is the position of the treatment in the pathway of care for the condition?	The Committee understood that ipilimumab would be valuable as a first-line treatment option for people with advanced (unresectable or metastatic) malignant melanoma. Ipilimumab is currently recommended by NICE as a second-line treatment for people with advanced (unresectable or metastatic) malignant melanoma.	4.1
Adverse reactions	The summary of product characteristics lists the following very common 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.	2.2

Evidence for clinical effectiveness		
Availability, nature and quality of evidence	There were no trials directly comparing ipilimumab 3 mg/kg monotherapy with the comparators in the scope: dacarbazine or vemurafenib. The Committee considered the manufacturer's response to consultation in which it proposed an alternative approach to assessing the clinical and cost effectiveness of 3 mg/kg ipilimumab monotherapy first-line. This method used data from the MDX010-20 trial adjusting overall survival curve to estimate the clinical effectiveness of 3 mg/kg ipilimumab first-line rather than using evidence from CA184-024. The Committee was aware that in the updated base-case analysis, the manufacturer used overall survival and progression-free survival rates for ipilimumab from the previous appraisal (TA268), and overall survival and progression-free survival for dacarbazine were taken from the CA184-024 trial. The data were then adjusted to take into account differences in the patient baseline characteristics. The Committee noted the ERG's concerns that the approach used by the manufacturer was inconsistent with the previous appraisal.	3.1 4.2, 4.10 4.9

Relevance to general clinical practice in the NHS	The Committee heard from clinical specialists that for patients who have BRAF V600 mutation-negative melanoma, dacarbazine is the only first-line treatment option currently available, and it has never been shown to have survival benefit. For patients who have BRAF V600 mutation-positive melanoma, the Committee heard that vemurafenib was likely to remain the standard first-line treatment option especially in those with a high disease burden, but understood that ipilimumab would be valuable as a first-line option in approximately 20–30% of patients with small-volume indolent disease for whom vemurafenib could be reserved as rescue treatment later in the pathway. The Committee heard from the clinical specialists that treatments would usually be more effective rather than less effective if used earlier in therapy, and that there was no biologically plausible reason for ipilimumab monotherapy at a dose of 3 mg/kg to be less effective when used first-line rather than second-line. The Committee heard from the clinical specialists that even though ocular melanoma is biologically different from cutaneous melanoma, patients are offered the same treatment options. The Committee concluded that patients with ocular melanoma could be included in the final guidance.	4.1 4.3 4.6
Uncertainties generated by the evidence	The Committee noted that during consultation, the manufacturer had accepted the Committee's reluctance to accept evidence from CA184-024 and the assumption of equivalent efficacy of 10 mg/kg ipilimumab plus dacarbazine and 3 mg/kg ipilimumab alone. The manufacturer therefore proposed an alternative approach to assessing the clinical and cost effectiveness of 3 mg/kg ipilimumab monotherapy first-line. This method used data from the MDX010-20 trial, which had been the pivotal trial for TA268. The Committee considered that this provided additional relevant evidence and agreed that the overall survival curves from CA184-024 and MDX010-20 were similar, with both demonstrating an approximate 10% long-term overall survival benefit.	4.2, 4.3

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No clinically relevant subgroups were identified.	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that both MDX010-20 and CA184-024 had demonstrated an overall survival gain for patients treated with ipilimumab, and that this gain was at least 3 months. The Committee discussed the evidence available for ipilimumab 3 mg/kg alone compared with vemurafenib in the BRAF V600 mutation-positive population. The Committee was aware that no data were available for a direct comparison and the manufacturer had attempted to conduct an indirect comparison using the CA184-024 and BRIM 3 trials in its original submission. After the manufacturer made several adjustments the Committee concluded that the data were suitable for estimating the clinical effectiveness of ipilimumab 3 mg/kg compared with vemurafenib.	4.4 4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer's original submission presented a semi-Markov partitioned survival model, using second-line active treatment (from the CA184-024 trial) and third-line best supportive care. For vemurafenib, data from the vemurafenib arm of the BRIM-3 trial were incorporated directly into the model. In response to the consultation, the manufacturer presented an updated base-case and ICERs using the 3-state model and adjusted overall survival curves. The manufacturer also carried out 2 modifications to enhance the validity of the sequential model. Firstly, the mortality hazard for third-line treatment was assumed to be the same as for second-line ipilimumab. The second modification involved the use of survival curves from the MDX010-20 trial, taking into account patient baseline characteristics from the CA184-024 trial, rather than the use of hazard ratios to estimate efficacy of second-line ipilimumab.	3.16, 3.18, 3.42, 3.43, 4.10

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee considered the manufacturer's response to consultation and the updated analyses using the adjusted overall survival curve from the second-line trial MDX010-20 to estimate the clinical effectiveness of 3 mg/kg ipilimumab first-line. The Committee was aware that in the updated base-case analysis, the manufacturer used overall survival and progression-free survival for ipilimumab from the previous appraisal (TA268), and overall survival and progression-free survival for dacarbazine were taken from the CA184-024 trial. The data were then adjusted to take into account differences in the patient baseline characteristics. The Committee noted concerns from the ERG that the approach used by the manufacturer was inconsistent with the previous appraisal.	4.9
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	EORTC-QLQ-30 utility data were collected in the CA184-024 trial but there were lower completion rates among surviving patients at certain time points. The ERG was concerned at the lack of direct EQ-5D data.	3.3, 3.31 3.31
Are there specific groups of people for whom the technology is particularly cost effective?	No. The clinical specialists stated that although it is not possible to identify patients most likely to experience a response with ipilimumab, it was associated with a very durable response in some patients whose condition responds to treatment.	4.1
What are the key drivers of cost effectiveness?	In the updated model, cost effectiveness was most affected by shortening the time horizon but generally the results were insensitive to changes. The Committee also noted that the use of a 3-state model, which the ERG preferred to the sequential modelling used in the manufacturer's original submission, and lower estimates of effectiveness for ipilimumab, produced substantially higher ICERs than in the original submission.	4.10

Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered the manufacturer's updated base-case results submitted in response to consultation. The Committee concluded that the most plausible ICER is £47,900 per QALY gained for ipilimumab compared with dacarbazine and £28,600 per QALY gained for ipilimumab compared with vemurafenib.	4.10
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer provided the same patient access scheme as agreed with the Department of Health for TA268.	-
End-of-life considerations	The Committee agreed that the life expectancy for people with advanced melanoma, particularly for those with distant metastases, was less than 24 months. The Committee also agreed that there was sufficient evidence to indicate that the treatment offers an extension to life of at least an additional 3 months, compared with current NHS treatment. The Committee heard from the clinical specialists that there are fewer than 1000 people in England with advanced melanoma who need first-line treatment. The Committee was satisfied that ipilimumab met the criteria for being a life-extending, end-of-life treatment and that the trial evidence presented for this consideration was robust.	4.13
Equalities considerations and social value judgements	No equalities issues were identified during the scoping exercise or appraisal process.	-

5 Implementation

5.1 The Department of Health and the manufacturer have agreed that ipilimumab will be available to the NHS with a patient access scheme which makes ipilimumab available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient

access scheme should be directed to [NICE to add details at time of publication]

5.2 NICE has developed tools [link to http://guidance.nice.org.uk/taXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.

- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee considered that more research is needed to establish the treatment sequence for vemurafenib and ipilimumab in patients who have BRAF V600 mutation-positive melanoma. This may provide important information about patient subgroups that should be targeted with the different treatments first-line. The Committee was aware that several trials were ongoing that explored treatment sequences relating to vemurafenib and ipilimumab and considered that these would be important. The Committee encouraged patient recruitment to these trials.

6.2 Further research into whether concomitant dacarbazine enhances the clinical effectiveness of ipilimumab would be encouraged because it could provide information for future treatment strategies, as would more data on the relative effectiveness of ipilimumab when given as a first-line or second-line treatment.

7 Related NICE guidance

Details are correct at the time of consultation. Further information is available on the NICE website.

Published

- Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance 268 (2012).
- Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. NICE technology appraisal guidance 269 (2012).

Under development

- Dabrafenib and trametinib for treating advanced unresectable or metastatic BRAF V600 mutation-positive melanoma. NICE technology appraisal guidance, publication expected September 2014.

8 Review of guidance

8.1 The guidance for this technology will be considered for review in June 2017. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, Appraisal Committee
May 2014

9 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)

Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice Chair)

Consultant Physician, University Hospitals of Leicester

Professor Thanos Athanasiou

Professor of Cardiovascular Sciences and Cardiac Surgery, Imperial College London; Consultant Cardiothoracic Surgeon, Imperial College Healthcare NHS Trust

Dr Graham Ash

Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Simon Bond

Senior Statistician, Cambridge Clinical Trials Unit

Professor Aileen Clarke

Professor of Public Health and Health Services Research, University of Warwick

Dr Andrew England

Lecturer in Medical Imaging, National Institute for Health Research (NIHR) Fellow, University of Liverpool

Adrian Griffin

Vice President, Health Technology Assessment (HTA) and International Policy, Johnson & Johnson

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital, Bristol

Dr Sharon Saint Lamont

Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, Health Economics Research Group (HERG), Brunel University

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Mohit Misra

GP, Queen Elizabeth Hospital, London

Ms Sarah Parry

CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees

Lay Member

Dr Ann Richardson

Lay Member

Ms Ellen Rule

Programme Director, NHS Bristol

Mr Stephen Sharp

Senior Statistician, Medical Research Council (MRC) Epidemiology Unit, University of Cambridge

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital

Dr Peter Sims

GP, Devon

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay Member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Caroline Hall

Technical Lead

Raisa Sidhu and **Sally Doss**

Technical Advisers

Bijal Joshi

Project Manager

10 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Centre for Reviews and Dissemination (CRD), Centre for Health Economics (CHE), University of York:

- Alison Eastwood, Claire McKenna, Ros Wade et al. Evidence Review Group's Final Report Ipilimumab for previously untreated unresectable malignant melanoma. December 2013.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- Bristol-Myers Squibb

II. Professional/specialist and patient/carer groups:

- British Association of Dermatologists
- British Association of Skin Cancer Nurse Specialists
- Melanoma Focus
- Melanoma UK
- OcuMel UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England

- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Centre for Reviews and Dissemination and Centre for Health Economics, University of York
- Commissioning Support Appraisal Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- MRC Clinical Trials Unit
- National Clinical Guideline Centre
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on ipilimumab by attending Committee discussions and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Mark Harries, Consultant Medical Oncologist, nominated by organisation representing Melanoma Focus – clinical specialist
- Dr Ruth Plummer, Consultant Medical Consultant and Clinical Professor of Experimental Cancer Medicine, nominated by organisation representing Royal College of Physicians – clinical specialist
- Richard Jackson, nominated by organisation representing National Collaborating Centre for Cancer – patient expert (first Committee meeting only)
- Gillian Nuttall, nominated by organisation representing Melanoma UK – patient expert (first Committee meeting only)

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Bristol-Myers Squibb