

# Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma

Technology appraisal guidance  
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# 1 Recommendations

- 1.1 Ipilimumab is recommended 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 Pharmaceuticals) 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 has a UK marketing authorisation for 'the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy'. For further information, see the summary of product characteristics.
- 2.2 Ipilimumab is most commonly associated with adverse reactions resulting from increased or excessive immune activity including 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 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, with a total of 4 doses for the full treatment course. 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'. Ipilimumab costs £3,750 for 50 mg and £15,000 for 200 mg (excluding VAT, BNF, September 2012). Assuming an average body weight of 70 kg, each dose of ipilimumab would need a 200 mg vial and a 50 mg vial costing £18,750. A 4-dose course would therefore cost £75,000, not including administration costs. Costs may vary in different settings because of negotiated procurement discounts. 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 size of the discount is commercial in confidence. 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 considered evidence submitted by the manufacturer of ipilimumab and a review of this submission by the Evidence Review Group (ERG).

- 3.1 The key evidence for the clinical effectiveness of ipilimumab came from 1 trial (MDX010-20), which assessed the efficacy and safety of ipilimumab in adults with advanced, unresectable stage 3 or stage 4 malignant melanoma who had been previously treated with interleukin-2, dacarbazine, temozolomide or other chemotherapies. This evidence was supported by results from a dose-ranging trial (CA 184-022), and a safety and tolerability trial (CA 184-007).
- 3.2 The MDX010-20 trial was an international, multicentre, double-blind, 3-armed, randomised, controlled trial. A total of 676 adults with advanced malignant melanoma were randomised to receive ipilimumab 3 mg/kg in combination with an investigational gp100 peptide vaccine ('ipilimumab plus gp100'; n=403), ipilimumab 3 mg/kg in combination with placebo ('ipilimumab alone'; n=137), or gp100 in combination with placebo ('gp100 alone'; n=136) every 3 weeks for 4 cycles. Approximately 38% of patients in the trial were from Europe, with 8% from the UK. The patients were all HLA-A\*0201 (human leukocyte antigen serotype group) positive and were generally well balanced for key baseline characteristics. At study entry, nearly all patients (98.2%) had stage 4 disease.
- 3.3 The primary outcome of the MDX010-20 trial was overall survival for people treated with ipilimumab plus gp100 compared with gp100 alone. Secondary outcomes in the trial included overall survival in people treated with ipilimumab plus gp100 compared with ipilimumab alone, best objective response rate, disease control rate, duration of response, progression-free survival, time to progression and health-related quality of life.
- 3.4 Results from the MDX010-20 trial showed that ipilimumab plus gp100 led to a statistically significant increase in median overall survival by approximately 3.5 months compared with gp100 alone (hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.55 to 0.85; p=0.0004). When ipilimumab alone was compared with gp100 alone, ipilimumab increased median overall survival by approximately 3.7 months (HR 0.66; 95% CI 0.51 to 0.87; p=0.0026). There was no statistically

significant difference in median overall survival between people treated with ipilimumab plus gp100 and those treated with ipilimumab alone (HR 1.04; 95% CI 0.83 to 1.30;  $p=0.7575$ ), which the manufacturer considered was evidence that gp100 did not influence the overall survival outcome when combined with ipilimumab treatment. Approximately 65% of people treated with an ipilimumab-containing regimen received all 4 doses of ipilimumab in line with the licensed regimen, and in this subgroup the median survival in both the gp100 and ipilimumab arms was greater than in those who received fewer than the full 4 doses. The differences in survival gain between the ipilimumab and gp100 arms were also more favourable in people treated with all 4 doses (results provided as academic in confidence). All response-related secondary outcomes (including best objective response rate and progression-free survival) showed positive results for people who received treatment with an ipilimumab-containing regimen compared with people who received gp100 alone.

- 3.5 The CA 184-022 trial was a double-blind, multicentre, dose-ranging, randomised, controlled trial that included 217 patients with previously treated, treatment-refractory or treatment-intolerant unresectable stage 3 or stage 4 melanoma. They were randomised to receive either ipilimumab 0.3 mg/kg, 3 mg/kg or 10 mg/kg every 3 weeks for 4 cycles followed by maintenance therapy every 3 months. The outcomes included estimated best objective response rate, progression-free survival at 24 weeks, median overall survival and duration of response. The CA 184-007 trial was a double-blind, multicentre, randomised, controlled trial. Patients ( $n=115$ ) with unresectable stage 3 or stage 4 melanoma who were treatment naive or who had been previously treated were randomised to receive open-label ipilimumab (10 mg/kg at weeks 1, 4, 7 and 10) with either concomitant oral budesonide or placebo. The outcomes included adverse reactions (specifically diarrhoea), best objective response rate, duration of response and overall survival.
- 3.6 The most common adverse reactions associated with ipilimumab treatment reported in the 3 trials included in the manufacturer's submission resulted from increased or excessive immune activity. They included diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain. These adverse reactions were considered to be generally medically manageable and usually reversible with topical and/or systemic immunosuppressants. Progressive disease was the most frequent reason for death in the MDX010-20 and CA 184-022

- studies. There were 14 (2.2%) adverse reactions with an outcome of death in the MDX010-20 trial that related to the study treatments; 8 deaths in the ipilimumab plus gp100 group, 4 in the ipilimumab alone group and 2 in the gp100 alone group. Of those deaths, 7 were associated with immune-related adverse reactions (including colitis, bowel perforation and organ failure): 5 in the ipilimumab plus gp100 group and 2 in the ipilimumab alone group.
- 3.7 The manufacturer undertook a systematic search and identified 10 economic evaluations in pre-treated or advanced melanoma. None of the studies evaluated ipilimumab. The manufacturer therefore submitted a de novo economic evaluation in which people treated with ipilimumab were compared with those who received best supportive care. There were 4 mutually exclusive states included in the model: baseline disease, non-progressive disease, progressive disease and death. All people were assumed to start in the baseline disease state (after chemotherapy), then at the end of each cycle they could move to the non-progressed health state or to the progressed health state, or they could die. The model used daily cycles for the first 5 years during the trial period, and weekly cycles thereafter for a lifetime (30 year) horizon. The perspective adopted in the economic evaluation was that of the NHS and personal social services, and costs and benefits were discounted at 3.5% per year.
- 3.8 The proportion of people in each health state was calculated using progression-free survival and overall survival data from the MDX010-20 trial. Data on progression-free survival and overall survival for people receiving best supportive care were not available directly from the trial. However, results from the trial showed that treatment with gp100 alone led to a median overall survival of 6.4 months, which was consistent with survival estimates achieved with best supportive care. Therefore, data from the gp100 arm of the trial were assumed by the manufacturer to be a proxy for the course of disease in people receiving best supportive care. Adverse-reaction rates for ipilimumab and best supportive care were estimated from the MDX010-20 trial. The resource costs included in the model were drug acquisition and administration costs, and the cost of the disease, which included costs related to each health state and of treating adverse reactions.
- 3.9 In the manufacturer's original submission, 2 approaches to parametric curve fitting for the survival modelling were presented. The first strategy involved a



single curve fit approach that showed that none of the curves fitted the Kaplan-Meier data from the MDX010-20 study. The second strategy involved using a 2-part curve fit in which the Kaplan-Meier estimates for overall survival and progression-free survival were used for the first 18 months and 'best-fit' parametric curves were used thereafter. The manufacturer concluded that the 'best-fit' curves were: exponential for progression-free survival in the ipilimumab arm, Gompertz for overall survival in the ipilimumab arm and exponential for overall survival in the best supportive care arm. Progression-free survival in the best supportive care arm was represented by the overall survival arm.

- 3.10 Health-related quality of life was measured in the MDX010-20 trial, which used the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the short form 36 (SF-36) questionnaires. The questionnaires were predominantly completed by trial participants at baseline and week 12, with only 26 questionnaires completed after week 12. For the economic analysis, utilities were obtained from responses to the EORTC QLQ-C30 from 971 trial observations using a recently developed preference-based version of the instrument. The utility values assumed for the progression-free disease and progressive disease health states in the model were 0.80 (95% CI 0.53 to 0.97) and 0.76 (95% CI 0.46 to 0.97) respectively. The manufacturer also conducted a systematic review to identify studies that included health-related quality-of-life data for people with metastatic melanoma. One study was identified that included 63 patients from the UK and 77 patients from Australia who valued 'vignettes' or descriptions of advanced melanoma health states developed by the researchers.
- 3.11 In the manufacturer's original base case, ipilimumab treatment led to an undiscounted incremental gain in overall survival of 33.8 months compared with best supportive care. The incremental cost-effectiveness ratio (ICER) for ipilimumab compared with best supportive care was £60,737 per quality-adjusted life year (QALY) gained (incremental cost of £83,351 and incremental benefit of 1.37 QALYs). This was based on the assumption that all patients received 3.3 doses of ipilimumab at 3 mg/kg body weight, corresponding with the average number of doses used in the clinical trial.
- 3.12 Probabilistic sensitivity analysis reported a 14% chance of ipilimumab being cost effective compared with best supportive care at £50,000 per QALY gained.

Deterministic sensitivity analyses showed that the ICER was sensitive to the utility values assumed for the progressive disease health state. An increase in this utility value reduced the ICER and conversely a reduction in utility increased the ICER. For example, using a lower utility (0.60) for progressive disease increased the base-case ICER to £73,854 per QALY gained. Structural sensitivity analysis also showed that decreasing the discount rate to 0% reduced the ICER from £60,737 to £42,871 per QALY gained because the long-term benefits of ipilimumab in the base case were discounted to a large degree, whereas costs of treatment were only incurred in the first year of the model, and therefore were unaffected by discounting.

- 3.13 The manufacturer also conducted scenario analyses to explore the effect on the ICER of assumptions about the amount of each dose of ipilimumab needed per patient and the possibility of vial sharing. Results from these analyses showed that the dose of ipilimumab given per patient has a large impact on the manufacturer's ICER, with the minimum dose given in the trial and compassionate use programme (3×50 mg) resulting in an ICER of £38,387 per QALY gained and the maximum dose (2×200 mg) given resulting in an ICER of £88,788 per QALY gained. In addition, the results showed that vial sharing has the potential to reduce the manufacturer's original base-case ICER to £55,824 per QALY gained.
- 3.14 The ERG reviewed the clinical-effectiveness evidence for ipilimumab and noted that none of the studies included in the manufacturer's submission compared ipilimumab with any of the comparators listed in the decision problem (best supportive care, carboplatin-based chemotherapy and dacarbazine). The ERG commented that the MDX010-20 study was well designed and that it was satisfied that the participants were representative of patients in UK clinical practice. The ERG expressed concern that the manufacturer considered gp100 clinically comparable to best supportive care because patient outcomes in the gp100 alone arm of the MDX010-20 study appeared less favourable than might be expected in untreated people.
- 3.15 The ERG commented that the clinical data provided by the manufacturer suggested that treatment with ipilimumab was associated with a long-term overall survival benefit over gp100 for a small number of patients. However, it noted that to date no patient characteristics or biomarkers have been identified that can prospectively identify the people most likely to benefit from treatment

with ipilimumab. The ERG noted that the European Medicines Agency considered a number of supplementary analyses carried out by the manufacturer in an attempt to identify possible subgroups of people who might (or might not) benefit from treatment with ipilimumab. However, the subgroups were small and the ERG determined that no conclusions could be drawn from this analysis.

- 3.16 The ERG considered that the manufacturer's model was well constructed, but it proposed a number of minor corrections and modifications, which resulted in a reduction in the base-case ICER from £60,737 to £54,462 per QALY gained. However, the ERG noted that the main weakness of the manufacturer's original model was the estimate of mean overall survival. The ERG acknowledged that the natural history and prognosis for metastatic melanoma is not well understood and the manufacturer claimed a substantial improvement in mean survival on the basis of results from a single trial. The ERG cited a study published in 1999 involving a re-analysis of 8 trials of interleukin-2 for people with metastatic melanoma. Of the patients, 80% died within 2 years but most of those surviving the 2-year follow-up period survived for a further 9 years. The ERG noted that this response pattern was replicated in the MDX010-20 study and suggested that this was likely to be because survival rates for people with advanced metastatic melanoma vary substantially. In light of this, it is possible that the data available for analysis are weakest when improved survival is likely to generate the most added life years from the treatment. The ERG therefore noted that, although the MDX010-20 trial used by the manufacturer showed a survival advantage for ipilimumab, it was unable to reliably quantify the long-term survival benefit.
- 3.17 The ERG had concerns about the manufacturer's interpretation of the MDX010-20 trial data. In particular, it noted that the fitted overall survival functions beyond 18-month follow-up generated mortality risks lower than those in the general (healthy) population at a comparable age and, as a consequence, the model predicted substantial numbers of people surviving to unreasonably advanced ages (beyond 100 years). To counter this anomaly, the manufacturer replaced the calculated model mortality risks with mortality risks experienced by the general population beyond 5-year follow-up. The ERG noted that this approach implied that anyone surviving beyond 5 years of second-line systemic treatment was effectively cured; however, no evidence was submitted by the manufacturer in the original submission to support this claim.

- 3.18 In an exploratory analysis, based on the manufacturer's original submission, the ERG adopted a pragmatic approach to model overall survival by calculating the area under the Kaplan-Meier curve to a common late time point beyond which both the ipilimumab and best supportive care arms could be seen to be following long-term trend lines. It then projected further life expectancy based on calibrating a parametric function. The results from this method suggested mean undiscounted life years of 11.2 months for gp100 alone and 27.4 months for the combined ipilimumab arms from the MDX010-20 trial, which equated to a mean gain in overall survival of 16.2 months. These results were noted to be less than half the value calculated in the base case of the manufacturer's original model (that is, a mean gain in overall survival of 33.8 months). Using the revised projections, the ERG noted that the manufacturer's original base-case ICER increased to £96,717 per QALY gained. The ERG stated that its exploratory analysis on overall survival cannot be considered definitive because the volume and duration of patient data available from the MDX010-20 trial were inadequate to achieve survival projections that can be used as a basis for decision-making. However, the ERG considered that the manufacturer's original model is likely to have overestimated the extent of survival benefit associated with treatment with ipilimumab, which would have a considerable effect on the ICER.
- 3.19 In response to consultation, the manufacturer offered an alternative approach to modelling long-term survival for people who are treated with ipilimumab. The manufacturer used a 3-part curve fit approach with Kaplan-Meier analysis results from MDX010-20 unmodified for the first 18 months, followed by a parametric model (Gompertz) fitted to the trial data from 18 months to 5 years and, thereafter, hazards derived from analysis of a malignant melanoma disease register modified by background mortality rates. The manufacturer used data from a published register of 1158 patients with stage 4 melanoma in the USA. The manufacturer used the survival curve from this analysis as the basis for estimating the extended survival of patients (beyond 5 years) in the MDX010-20 trial. This was further modified to include age-related mortality because the register data included melanoma-related death only. In this revised model the survival estimates were further adjusted, using a Cox proportional hazards regression, to reflect the difference in overall survival for long-term survivors in the combined ipilimumab treatment groups (ipilimumab alone and ipilimumab plus gp100) and the gp100 alone group (HR 0.782). By including this revised approach in the model, the estimated survival gain for people treated with ipilimumab was

30.0 months (compared with their original estimate of 33.8 months).

- 3.20 The Department of Health agreed a patient access scheme in which a simple discount is applied to the list price of ipilimumab. For the analyses including the scheme, the manufacturer presented additional survival data from 3 smaller trials (CA 184-007, CA 184-008 and CA 184-022: all individual parent studies included in CA 184-025) comprising patients who initially received 0.3 mg/kg, 3 mg/kg or 10 mg/kg dosages of ipilimumab. The manufacturer identified 72 patients from a dose-ranging study (CA 184-022), who had received previous treatment and then ipilimumab at the licensed dose of 3 mg/kg. These were considered to be comparable to the patients treated with ipilimumab in the MDX010-20 trial, and the manufacturer presented a pooled analysis of the MDX010-20 trial patients supplemented by these patients from the CA 184-022 trial. The manufacturer also proposed a broader pooling of all data from patients treated with ipilimumab, regardless of dosing level. The manufacturer stated that these additional data, which provided follow-up information on patients treated with ipilimumab for between 50 and 70 months, confirmed the long-term effect of ipilimumab at all dosages.
- 3.21 The manufacturer's revised base-case analysis was calculated using the 3-part curve fit approach, the patient access scheme, and trial data for patients receiving the 3 mg/kg dose of ipilimumab in the MDX010-20 trial pooled with 72 patients from the CA 184-022 dose-ranging trial receiving the same dose. This resulted in a revised base-case deterministic ICER of £46,739 per QALY gained for ipilimumab compared with best supportive care. Using only the MDX010-20 trial data, the ICER was £42,211 per QALY gained. The manufacturer considered that the probabilistic sensitivity analyses showed a low level of parameter-related uncertainty around the baseline ICER and reported that there was an approximately 81% chance that the ICER for ipilimumab would be less than £50,000 per QALY gained when the patient access scheme was included.
- 3.22 The manufacturer conducted structural sensitivity analyses and scenario analyses exploring the impact of alternate curve fits, varied cut-off points in the 3-part curve fit approach, alternative sources of observational data and the use of the ERG approach on the overall survival benefit of ipilimumab. The manufacturer stated that the only scenario in which the ICER rose above £50,000 per QALY gained was when the manufacturer adopted the ERG approach for

survival estimation, which resulted in an ICER of £55,807 per QALY gained. Further scenario analyses involved excluding patients who crossed over between different doses of ipilimumab and resulted in a nominal reduction in the ICER to £44,426 per QALY gained. The manufacturer stated that the areas identified as potentially problematic by the ERG, such as cut-off points and sources of observational data, did not have a large impact on the ICER, and that the increased patient numbers and number of trials with similar results reduced the uncertainty associated with the estimation of longer-term survival.

- 3.23 The manufacturer noted that, although the summary of product characteristics for ipilimumab does not recommend vial sharing, discussions with clinicians indicated that vial sharing may be possible in some clinical centres in the UK. The manufacturer provided scenario analyses to explore the impact of vial sharing and noted that, if 50% of ipilimumab wastage was avoided through vial sharing, then the revised base-case ICER would be reduced. The manufacturer also suggested that, if drug-specific utilities were used instead of pooled utilities (which were used in the original economic model), then the revised base-case ICER would decrease further.
- 3.24 The manufacturer conducted sensitivity analyses using the discount rate of 1.5% for costs and benefits, and also a discount rate of 3.5% for costs and 1.5% for benefits. These resulted in ICERs of £39,714 and £38,323 respectively per QALY gained. The manufacturer's probabilistic sensitivity analysis indicated that, in these scenarios, the ICER for ipilimumab is 94% and 100% likely to be less than £50,000 per QALY gained respectively.
- 3.25 The ERG considered the manufacturer's revised long-term survival projections submitted in response to consultation. It believed that the main weakness of the manufacturer's survival model was in not providing a rationale, other than replicating the observed data, to support the division of data into 3 time periods and the use of different methods in each period. Furthermore, there were substantial differences between the populations in the MDX010-20 trial and the disease register in terms of patients' initial diagnosis, treatment history and time from initial diagnosis. The ERG also considered that the manufacturer's approach to deriving the long-term hazard ratio was problematic because of the small number of people in the analysis for the gp100 group in the trial (n=19) and the fact that the long-term survival trends were established much earlier in the gp100



group (about 300 days) than in the combined ipilimumab treatment group (about 750 days), which could lead to bias in the hazard ratio. In light of these concerns, the ERG considered that the survival projections presented by the manufacturer in response to consultation were uncertain.

- 3.26 The ERG reviewed the manufacturer's assumptions about vial sharing. It considered that although vial sharing is theoretically possible, in reality it would be difficult to implement because only 250 to 300 people nationally will need treatment each year, which only equates to 1 to 2 people in each centre each month. Therefore, the ERG was not convinced that any specialist centre could achieve regular savings in ipilimumab costs from organised vial sharing.

## **ERG comments on manufacturer's additional analyses (including the patient access scheme)**

- 3.27 The ERG reviewed the manufacturer's alternative data sets based on the pooling of selected data from several smaller clinical studies with data from the main MDX010-20 trial. The ERG thought that the patient population was too dissimilar to the MDX010-20 trial to allow direct comparison, and that not all studies involved the dosing regimen of ipilimumab (3 mg/kg) for which marketing authorisation has been granted. Therefore, the ERG considered that the broader pooling of data from all patients who received ipilimumab, regardless of dosing regimen or patient baseline characteristics, would lead to uninterpretable results.
- 3.28 Regarding the pooling of 3 mg/kg data from the MDX010-20 trial and the CA 184-022 study, the ERG thought that pooling isolated treatment arms across trials was inappropriate because it would break randomisation and therefore invalidate any comparison between the intervention treatment and the comparator. Furthermore, there were no equivalent comparator treatment arms available in the CA 184-022 study to balance the pooling of the ipilimumab trial arms. Finally, the ERG thought that the additional data from the CA 184-022 study did not extend the length of follow-up beyond that in the MDX010-20 trial, and therefore did not reduce the uncertainty surrounding long-term outcomes. Therefore, the ERG considered that it was only appropriate to include data from the MDX010-20 trial. Consequently, the ERG found that the patient access

scheme would decrease the ICER for ipilimumab compared with best supportive care to £66,520 per QALY gained.

- 3.29 However, the ERG carried out further analyses aimed at clarifying the possible mechanisms underlying the pattern of overall survival observed in the clinical trials and disease registers for patients with advanced malignant melanoma. The ERG proposed a hypothesis assuming that patients with advanced malignant melanoma are drawn from 2 distinct subgroups of unknown aetiology and that each subgroup is characterised by a separate hazard rate that does not vary over time. Based on this, a mixed exponential distribution for overall survival, which consisted of the proportion of the population comprising one of the subgroups and separate hazard rates for each of the subgroups, was considered appropriate. The ERG tested this approach by applying it to published results from 2 large patient registries, which resulted in strong correspondence to the observed data in both data sets and for each disease stage. The results of this method of projecting overall survival in the submitted model, using only the MDX010-20 trial data, resulted in a mean gain in overall survival of 20.9 months. Using this method, combined with the patient access scheme, resulted in an ICER of £58,590 per QALY gained. The ERG's revised approach implies that patients fall into 2 distinct groups in relation to mortality risk, but currently no direct evidence is available to explain how such a differentiation may occur. The ERG also noted that the melanoma databases used in testing the revised approach featured patients from the time of diagnosis, but their use in modelling (both by the manufacturer and by the ERG) began at the time of randomisation, at which point patients may have survived several years of treatment. As a result, direct use of database trends could be misleading.
- 3.30 Full details of all the evidence are in the manufacturer's submission, the ERG report, the manufacturer's response to the appraisal consultation document, further evidence and analyses, and the ERG's critique of the manufacturer's responses.



## 4 Consideration of the evidence

- 4.1 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.
- 4.2 The Committee heard from the clinical specialists that they considered ipilimumab to represent a 'step-change' in the treatment of advanced melanoma and that it is the first new treatment available in 30 years that may offer clinical benefit and possible long-term survival gain for people with advanced, unresectable disease that has progressed after first-line therapy. Other drugs are also in development. The Committee heard that the optimal place for ipilimumab treatment in the clinical pathway for advanced (unresectable or metastatic) melanoma was still being debated in the clinical community. However, the Committee understood that most clinicians in the UK would use ipilimumab as a second-line treatment in line with its UK marketing authorisation. The Committee heard from a patient expert that unresectable melanoma substantially worsens quality of life and, without effective new therapies, the prognosis for advanced disease is very poor. The Committee concluded that there was a significant unmet need for effective therapies in this patient population.
- 4.3 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of ipilimumab. It noted that the manufacturer derived efficacy data primarily from the MDX010-20 trial, which showed that treatment with ipilimumab led to a statistically significant median overall survival gain of approximately 3.7 months (HR 0.66; 95% CI 0.51 to 0.87;  $p=0.0026$ ) compared with gp100 for people with progressive disease after first-line therapy. The Committee heard from the clinical specialists that people treated with ipilimumab will have some survival benefit, but only 10% of people may experience long-term benefits. The Committee was aware that the trial length was 56 months, and that survival benefit was demonstrated for the length of the trial, but that there was uncertainty about continuing benefit thereafter. The clinical specialists indicated that melanoma may have an unpredictable clinical course and that late

recurrences are well recognised. The Committee noted that a curative treatment would be expected to result in the disappearance of all visible disease (complete response), but less than 1% of patients in the ipilimumab arms of the MDX010-20 trial showed a complete disease response. In addition, although there was trial evidence of some people whose disease remained stable after being treated with ipilimumab, it was not clear how prolonged that response might be. The clinical specialists agreed that it is too early to regard this as a curative treatment.

4.4 The Committee further considered the additional data presented by the manufacturer. These data were presented to provide further evidence of the survival benefit of ipilimumab over a period of 50 to 70 months' follow-up, and to supplement the evidence from the MDX010-20 trial. The Committee agreed that these additional data supported the findings in the MDX010-20 trial, but agreed with the ERG that the pooling of these additional data with data from the MDX010-20 trial was inappropriate and should not be included in the economic modelling. The Committee concluded that the evidence on the clinical effectiveness of ipilimumab was robust for a period of at least 5 years, and that a small proportion of patients were likely to benefit from ipilimumab in the long term.

4.5 The Committee considered the adverse reactions associated with treatment with ipilimumab. The Committee understood from the clinical specialists and patient experts that people being treated with ipilimumab can have immune-related adverse reactions, which have a substantial negative impact on their quality of life. The Committee noted that 12 deaths related to treatment with ipilimumab occurred in the MDX010-20 trial, but heard from the clinical specialists that subsequent trials of ipilimumab as first-line treatment have not reported any treatment-related deaths. The clinical specialists considered that this indicated that, as experience with ipilimumab grows, adverse reactions will be more quickly identified and treated. The Committee also heard from the patient experts that the possible survival benefits from adhering to treatment with ipilimumab outweigh the severe adverse reactions. The Committee concluded that although the adverse reactions and mortality associated with ipilimumab seen in the MDX010-20 trial were considerable, most adverse reactions, including those that led to hospital admission, were manageable and would be managed more effectively as clinicians become familiar with ipilimumab's toxicity profile. It also concluded that people may be willing to tolerate considerable toxicity if there are

potential survival benefits.

- 4.6 The Committee noted that the UK marketing authorisation for ipilimumab stipulates that people should receive all 4 doses of treatment, even if the disease appears to progress during treatment. The Committee heard from the clinical specialists that late responses to treatment have been reported. It heard that people should therefore continue to be treated unless their disease progresses to a degree that a response is very unlikely, or the side effects become intolerable. The Committee also understood from the clinical specialists that, although it is not possible to predict how a person's condition might respond to ipilimumab, people who experience a substantial decrease in performance status while receiving treatment are likely to have rapidly progressive disease and will not benefit from continued use of ipilimumab. The clinical specialists indicated that despite guidance on the use of all 4 doses, normal clinical evaluation and discussion with patients would be carried out to determine whether or not it was reasonable to continue with treatment. The Committee noted that approximately 65% of people treated with ipilimumab in the MDX010-20 trial received all 4 doses of treatment. They also heard from the clinical specialists that it is likely that more than 65% of people treated with ipilimumab in clinical practice would receive all 4 doses. The Committee concluded that it was reasonable to assume that not all patients would receive 4 doses of ipilimumab in clinical practice despite the administration advice in the UK marketing authorisation.
- 4.7 The Committee discussed the cost-effectiveness estimates from the manufacturer's original and revised economic models, the assumptions on which these were based, and the ERG's critique and exploratory analyses. The Committee noted that the manufacturer assumed that the gp100 vaccine was clinically comparable to best supportive care and used the efficacy estimates from the gp100 arm in the MDX010-20 trial to inform model inputs. The Committee understood from the clinical specialists that, although studies of vaccines (other than gp100) in people with advanced and metastatic melanoma have shown a survival disadvantage, there is no evidence that this occurs for people treated with gp100. The Committee agreed with the clinical specialists that gp100 is likely to be an acceptable proxy for best supportive care in the model.
- 4.8 The Committee heard from the manufacturer that EORTC-QLQ and SF-36 data

were collected in the MDX010-20 trial. It noted the ERG's concerns that the number of respondents to the questionnaires dropped off considerably after week 12 in the MDX010-20 trial and that there was little difference between the utilities assigned to the progression-free and the progressive disease health states. The Committee noted that additional sensitivity analyses conducted by the manufacturer in response to the appraisal consultation document showed that the utility assumed for the progressive disease state was not a major driver of cost effectiveness. The Committee concluded that the utility estimates derived by the manufacturer were acceptable.

4.9 The Committee noted that the length of follow-up in the MDX010-20 trial was too short to provide robust evidence of the overall survival gain beyond the length of the trial. The Committee expressed confidence in the data from the MDX010-20 trial, supported by data from 3 smaller trials, but noted that beyond this time period the calculation of overall survival gain was dependent on the modelling approach used for extrapolation. It was aware that the manufacturer and the ERG had each presented 2 different approaches. The manufacturer considered that the ERG's initial approach overestimated survival in the short term and underestimated it in the long term, such that the survival curve for the 3 mg/kg ipilimumab dose was below that seen in the observational data, which the Committee considered was implausible. The ERG considered that its updated approach using a mixed exponential approach better fitted the data than the manufacturer's model. The Committee accepted that the MDX010-20 trial showed that ipilimumab provides a 3.7 month median increase in overall survival when compared with best supportive care. However, when taking into account the small number of long-term survivors, there is a substantial degree of uncertainty about the modelling of long-term survival benefits.

4.10 The Committee considered the revised base-case ICERs presented by the manufacturer, taking into account the patient access scheme. The Committee noted that the manufacturer's base-case ICER based on the pooled 3 mg data and its preferred modelling approach was £46,700 per QALY gained and that there was an 81% probability of ipilimumab being cost effective if the maximum acceptable ICER was £50,000 per QALY gained. The ICER showed relatively little change when re-evaluated using a single curve fit, or sensitivity analyses changing the cut-off points in the 3-part model. The ICER, however, rose to £55,800 per QALY gained when the manufacturer used the ERG's prior overall

survival modelling approach. The Committee also noted that, when data from only the pivotal MDX010-20 trial were included, the manufacturer's ICER was £42,200 per QALY gained. The corresponding ICER calculated by the ERG using their preferred mixed exponential approach was £58,600 per QALY gained. The Committee previously considered (see section 4.4) that pooling of the 3 mg/kg data from the CA 184-022 trial with data from the MDX010-20 trial was inappropriate, and therefore only the ICERs calculated using the MDX010-20 data alone were appropriate for further consideration. It therefore gave further consideration to the manufacturer's ICER of £42,200 per QALY gained and the ERG's updated preferred estimate of £58,600 per QALY gained. The Committee appreciated that the correct modelling approach was uncertain, but found no evidence to indicate that the ERG's approach was based on more plausible assumptions than the manufacturer's approach. The Committee concluded that the manufacturer's ICER of £42,200 per QALY gained was a plausible estimate.

- 4.11 The Committee considered the manufacturer's additional scenario analysis on vial sharing and noted that, if it was assumed that 50% of ipilimumab wastage could be avoided, the manufacturer's revised base-case deterministic ICER reduced by approximately £2,000 per QALY gained (patient access scheme included). The Committee heard from the clinical specialists that it may be possible to avoid some wastage through vial sharing, particularly in the largest specialist centres, but that the manufacturer's estimate of 50% was overly optimistic. The Committee acknowledged that, although vial sharing may lead to cost savings in some specialist centres, this could be associated with additional administrative costs and logistic difficulties, and therefore it concluded that overall the impact of vial sharing on the cost effectiveness of ipilimumab was likely to be minimal.
- 4.12 The Committee considered whether it would be appropriate to consider sensitivity analyses on the discount rates used in the model and their effects on the revised ICER. The Guide to the methods of technology appraisal clarification issued by the Board of NICE states that 'where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for health effects and 3.5% for costs'. Having referred to this clarification, the Committee considered that substantial restoration of health for a very long period equated to restoration of health to the extent that

the person could be considered as having been effectively cured of their condition. It then considered whether ipilimumab is a treatment given with curative intent. It heard from the clinical specialists that unresectable malignant melanoma that has progressed on previous therapy is not considered to be curable. The Committee noted that a curative treatment would be expected to result in the disappearance of all visible disease (complete response), but that less than 1% of patients in the ipilimumab arms of the MDX010-20 trial showed a complete disease response. In addition, although there was trial evidence of some people whose disease remained stable after being treated with ipilimumab, it was not clear how prolonged that response might be. The clinical specialists agreed that it is too early to regard this as a curative treatment. The Committee concluded that evidence that ipilimumab was a curative treatment was lacking, and that it was unlikely to have substantial benefits for at least 30 years. The Committee therefore concluded that there was no case for differential discounting to be applied.

4.13 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.

4.14 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, particularly for those with distant metastases, as reflected in the trial population, 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 approximately 400 to 500 people with advanced melanoma that has progressed after chemotherapy each year in the UK, which represents a small patient population. Therefore, 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.

4.15 The Committee was mindful that [NICE's Guide to the methods of technology appraisal](#) states that a strong case should be identified for accepting an ICER that is higher than £30,000 per QALY gained. The Committee noted that in these circumstances the NICE methods guide states that judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of:

- the degree of certainty around the ICER
- any strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured
- whether the innovative nature of the technology adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure.

Furthermore, the Committee was aware of NICE's response to [Sir Ian Kennedy's report Appraising the value of innovation and other benefits](#), which states that when considering a technology identified as having innovative characteristics, the Appraisal Committee should satisfy itself that:

- it can be regarded as a 'step-change' in the management of the condition, **and**
- either that the identified innovative characteristics have been taken into account in the QALY calculation (in other words, that their impact on health-related quality of life has been fully captured) or, if not, that they have been

separately evaluated including their impact (if any) on the Committee's judgement of the most plausible ICER.

- 4.16 Having accepted that the supplementary advice for appraising a life-extending end-of-life treatment applies, and that the manufacturer's ICER of £42,200 per QALY gained was plausible, but also recognising that it could be higher using other approaches to modelling overall survival, the Committee considered whether ipilimumab could be considered a cost-effective use of NHS resources. On balance, the Committee considered that, given the robust clinical data available for a period of 50 to 70 months, the likelihood of long-term effectiveness in a small proportion of patients and the innovative nature of ipilimumab, it could be concluded that ipilimumab is a cost-effective use of NHS resources.
- 4.17 The Committee discussed whether the assessment of the change in health-related quality of life had been adequately captured in the economic analysis. It heard from a patient expert that people who are successfully treated, although in the minority, could lead an active and fulfilling life and were able to contribute to society. The Committee accepted that ipilimumab represents a valuable new therapy and that the mechanism of action is novel. It acknowledged that few advances had been made in the treatment of advanced melanoma in recent years and ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need. Nevertheless, the Committee considered that the clinical benefit of ipilimumab had been fully captured in the QALY calculation and concluded that, with the patient access scheme applied to the cost of ipilimumab, it had been demonstrated to be a cost-effective use of NHS resources for the treatment of advanced (unresectable or metastatic) malignant melanoma for people who have received prior therapy.



## 5 Implementation

- 5.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The [NHS England Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 5.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 5.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has previously treated advanced (unresectable or metastatic) melanoma and the healthcare professional responsible for their care thinks that ipilimumab is the right treatment, it should be available for use, in line with NICE's recommendations.

## 6 Recommendations for further research

- 6.1 Currently, there is an ongoing trial investigating the immunogenicity and analysing biomarkers in people receiving neoadjuvant ipilimumab treatment for melanoma. There is also a trial analysing tissue and blood biomarkers from people with stage 3 or stage 4 melanoma treated with ipilimumab with or without granulocyte-macrophage colony-stimulating factor.
  
- 6.2 The Committee noted the fact that no biomarkers have yet been identified in people with melanoma in whom ipilimumab had a long-term benefit. The Committee considered that further research should be conducted to identify biomarkers or patient characteristics in people who receive long-term benefit from ipilimumab. These biomarkers or patient characteristics could lead to a better targeted treatment pathway that would improve outcomes for people with melanoma. Furthermore, the Committee considered that, with the subsequent advent of melanoma treatments for specific mutations, further research should be conducted to assess the impact of ipilimumab on subgroups based on mutation type.

# 7 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

### **Professor Iain Squire (Vice Chair)**

Consultant Physician, University Hospitals of Leicester

### **Professor A E Ades**

Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

### **Professor Thanos Athanasiou (from September 2012)**

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

### **Dr Jeremy Braybrooke**

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

**Dr Gerardine Bryant (from September 2012)**

General Practitioner, Heartwood Medical Centre, Derbyshire

**Dr Fiona Duncan**

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

**Mr Andrew England (from September 2012)**

Lecturer in Medical Imaging, NIHR Fellow, University of Liverpool

**Mrs Eleanor Grey**

Lay Member

**Mr Adrian Griffin**

Vice President, HTA and International Policy, Johnson & Johnson

**Professor Jonathan Grigg**

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

**Dr Brian Hawkins (from September 2012)**

Chief Pharmacist, Cwm Taf Health Board, South Wales

**Dr Peter Heywood**

Consultant Neurologist, Frenchay Hospital

**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, 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 (from September 2012)**

General Practitioner, Queen Elizabeth Hospital, London

**Ms Sarah Parry (from September 2012)**

CNS Paediatric Pain Management, Bristol Royal Hospital for Children

**Ms Pamela Rees**

Lay Member

**Dr Ann Richardson**

Lay Member

**Dr Paul Robinson**

Medical Director, Merck Sharp & Dohme

**Ms Ellen Rule (from September 2012)**

Programme Director, NHS Bristol

**Mr Stephen Sharp**

Senior Statistician, MRC Epidemiology Unit

**Dr Peter Sims (from September 2012)**

General Practitioner, Devon

**Mr Cliff Snelling**

Lay Member

**Dr Eldon Spackman**

Research Fellow, Centre for Health Economics, University of York

**Mr Mike Spencer**

Assistant Director Patient Experience, Cardiff and Vale University Health Board

**Mrs Amelia Stecher**

Associate Director of Individual Funding Requests and Clinical Effectiveness, NHS Kent and Medway

**Mr David Thomson**

Lay Member

**Mr William Turner**

Consultant Urologist, Addenbrooke's Hospital

**Dr Luke Twelves (until April 2012)**

General Practitioner, Ramsey Health Centre, Cambridgeshire

**Dr John Watkins**

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

**Dr Anthony S Wierzbicki (until September 2012)**

Consultant in Metabolic Medicine and Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

**Dr Olivia Wu (from September 2012)**

Reader in Health Economics, University of Glasgow

## **NICE project team**

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

**Richard Diaz**

Technical Lead

**Fiona Rinaldi (until August 2012)**

Technical Adviser

**Raisa Sidhu (from August 2012)**

Technical Adviser

**Bijal Joshi**

Project Manager

## 8 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):

- Dickson R, Boland A, Bagust A et al. Ipilimumab for previously treated unresectable malignant melanoma: a single technology appraisal (August, 2011)

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). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Bristol–Myers Squibb Pharmaceuticals

Professional or specialist and patient or carer groups:

- British Association of Dermatologists
- Factor 50
- Macmillan Cancer Support
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Skin Care Campaign

Other consultees:



- Department of Health
- Welsh Government

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

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Care Improvement Scotland
- LRiG, The University of Liverpool
- National Collaborating Centre for Cancer
- National Institute for Health Research Health Technology Assessment Programme

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor 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 Paul Lorigan, Consultant Medical Oncologist, nominated by the organisation representing Skin Care Campaign, Factor 50, and Bristol–Myers Squibb – clinical specialist
- Dr Paul Nathan, Consultant Medical Oncologist, nominated by the organisation representing Skin Care Campaign, and Factor 50 – clinical specialist
- Mr Richard Jackson, nominated by the organisation representing Skin Care Campaign – patient expert
- Ms Gillian Nuttall, CEO and Founder of Factor 50, nominated by the organisation representing Factor 50 – patient expert

Representatives from the following manufacturer or 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 Pharmaceuticals

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