NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Ipilimumab for previously untreated advanced malignant melanoma [ID74]

[redacted]

The Evidence Review Group, Centre for Reviews and Dissemination University of York, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 16th October 2013 by Bristol Myers Squibb. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **21st November 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

[redacted]

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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SECTION A: CLARIFICATION ON EFFECTIVENESS DATA

Further study reports required

A1. Please provide any additional efficacy, safety and survival data from the two ongoing, retrospective, observational studies (CA184-332 and CA184-338) that may be available.

CA184-024 trial

A2. **PRIORITY REQUEST:** Please provide a comparison of ipilimumab 3mg/kg and ipilimumab 10mg/kg in both the treatment-naïve subgroup population and the whole population (both previously treated and untreated) in all trials. For example, please provide the Kaplan-Meier curve for overall survival (OS) and progression-free survival (PFS) comparing ipilimumab 3mg/kg with 10mg/kg in the CA184-004 and CA184-022 trials for the whole population as presented for TA268. Please refer to Figures 2 and 3 of 'Updated analysis with revised patient access scheme for ipilimumab for previously treated unresectable malignant melanoma', submitted by Bristol Myers Squibb on 17th August 2012 (accessed at http://guidance.nice.org.uk/TAG/208/FAD/RevisedPASBMS/pdf/English).

A3. **PRIORITY REQUEST:** Please provide justification for the assumption that concomitant DTIC therapy with ipilimumab 10mg/kg in the CA184-024 trial has no influence on the clinical efficacy of ipilimumab 10mg/kg monotherapy.

Please justify this assumption in light of the evidence presented in Table 16 from the MDX010-08 trial, which shows that ipilimumab 3mg/kg + DTIC has a lower hazard of death than ipilimumab 3mg/kg monotherapy, and in conjunction with the assumption that ipilimumab 3mg/kg is clinically equivalent to ipilimumab 10mg/kg.

A4. **PRIORITY REQUEST:** Please provide justification for the assumption that a fixed induction dose of ipilimumab 3mg/kg every three weeks for 12 weeks is clinically equivalent in terms of OS and PFS to maintenance therapy of ipilimumab given to responders every 12 weeks in the CA184-024 trial.

A5. **PRIORITY REQUEST:** If available, please provide data on the BRAF V600 status of participants in the CA184-024 trial.

A6. **PRIORITY REQUEST:** Please provide a breakdown of the reasons for non-completion of the EORTC QLQ-C30 questionnaire by treatment and at each time point (Table 17, page 70).

A7. Please provide further information about treatment discontinuations due to study-drug toxicity.

How many patients received one dose, two doses, three doses and all four doses of ipilimumab 10mg/kg induction therapy? Were there any dosage adjustments/breaks in treatment due to toxicity?

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A8. Table 26 on page 94 states that 18.2% ipilimumab plus DTIC patients and 25.5% DTIC patients had an adverse event (AE) with outcome of death (although not related to the study drug). Please provide further details.

A9. **PRIORITY REQUEST:** On page 96 the text states that "Subjects who survived more than 2 years from study entry and who had discontinued ipilimumab experienced few new onset immune-related AEs (or repeat occurrence if the same toxicity was also reported on study) more than 70 days after last dose, most of which were low grade in severity". Please provide more specific data; i.e. how many patients who survived more than 2 years from study entry experienced new onset immune-related AEs more than 70 days after the last dose, what were those adverse effects and what was the grade.

A10. **PRIORITY REQUEST:** Please provide further data on all adverse effects occurring after the on-study period (rather than just immune-related AEs). Please provide this data for patients who did not survive more than 2 years from study entry, as well as for those who did.

BRIM-3 Trial

A11. Please provide confidence intervals for the median overall survival figures presented in column 3, Table 16, page 69, for the BRIM-3 trial.

Network meta-analysis

A12. **PRIORITY REQUEST:** The CA184-024 trial included patients irrespective of BRAF V600 mutation status, whilst the BREAK-3 and BRIM-3 trials only included patients that tested positive for the BRAF V600 mutation. Please give your reasoning for including these trials in the same meta-analysis despite this difference in the inclusion criteria.

Search strategy

A13. The search strategies reported for the clinical evidence searches show that the results have been limited to randomised controlled trials and systematic reviews. It would be helpful to know which study design search filters for RCTs and systematic reviews have been used for MEDLINE, EMBASE and CINAHL? (10.2 Appendix 2, pages 243-248).

A14. **PRIORITY QUESTION:** Given the search strategy study design limits, how was the non-RCT evidence (listed in Table 9, page 43) identified? Did you specifically search for non-RCT evidence? If so, please provide details of the relevant search strategies.

A15. In section 10.2.5, page 248, under details of additional searches, it states that additional searches were conducted in clinicaltrials.gov. Is the search strategy used for clinicaltrials.gov available?

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A16. In section 10.2.5, page 248, under details of additional searches, only 3 conference proceedings are listed as being searched, however under the description of the searches for clinical evidence on page 35, there are 5 sources listed. Please could the sources searched be clarified?

A17. Please justify the inclusion of dabrafenib in the eligibility criteria used in the clinical search strategy (Table 5, page 37), when it is not one of the comparators listed in the NICE scope and decision problem (Table 4, page 32).

SECTION B: CLARIFICATION ON COST EFFECTIVENESS DATA

Economic model

B1. **PRIORITY REQUEST:** Please explain the rationale for modelling the cost-effectiveness of ipilimumab for previously untreated melanoma using a treatment sequencing approach. Additionally:

a) Please clarify whether the five-year survival curves for ipilimumab and DTIC in the CA184-024 trial already take account of progression to next line therapies.

b) Please present a graphical comparison of the five-year survival curves for ipilimumab and DTIC from the CA 184-024 trial and the five-year survival estimates for ipilimumab derived from the economic model.

c) Please provide the rationale for not using a three-stage model structure for progression-free survival, post-progression survival and death as used in the previous appraisal of ipilimumab for second line treatment of advanced stage melanoma.

d) To help support internal/external validation of the current approach, please consider presenting the cost-effectiveness results for ipilimumab using a three-stage model without including sequencing of treatment, that is, the model previously used in Technology Appraisal 268, 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'.

B2. Please provide justification for the choice of modelled treatment pathways of care as presented in Figure 26.

Please explain why all possible treatment permutations were not considered. For example, DTIC first line followed by vemurafenib second line is not considered as an option in the model but it is presented as an option in the current clinical care pathway shown in Figure 2.

B3. **PRIORITY QUESTION:** For the comparison of ipilimumab with vemurafenib in BRAF V600 mutation-positive patients, please explain why the hazard ratio for OS determined using the MTC analysis (Figure 18) was not used in the modelling. The HR of 1.16 suggests that ipilimumab + DTIC therapy is less effective than vemurafenib

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but the extrapolation using independent arms of the CA184-024 (ipilimumab + DTIC) and BRIM-3 (vemurafenib) trials in the modelling shows higher QALYs with ipilimumab compared with vemurafenib.

a) Please provide an explanation for this difference and the rationale for using independent arms of two different clinical trials.

b) Please estimate the implied HR for OS for the comparison of ipilimumab versus vemurafenib in the modelled extrapolation that uses independent arms by assuming no difference in efficacy for DTIC in the CA184-024 and BRIM-3 trials.

B4. Please clarify how progression on ipilimumab before the end of the 3 month treatment induction phase is modelled. Is the PFS curve for ipilimumab only used after the first 12 weeks?

Survival analysis

B5. Please provide the Kaplan-Meier curve for PFS of patients enrolled in the MDX010-08 trial for ipilimumab 3mg/kg and ipilimumab 3mg/kg + DTIC as presented in Figure 12 for overall survival.

B6. Please provide the hazard ratio with 95% confidence interval for PFS in the CA184-024, MDX010-08, and BRIM-3 trials as presented in Table 16 for overall survival.

B7. **PRIORITY QUESTION:** Please provide justification for the method used to estimate OS and PFS on second line treatment.

a) Please explain the rationale for estimating second line survival curves by adjusting the first line survival curves downwards by an apparently arbitrary hazard ratio.

b) Please provide the justification for not using the OS and PFS curves from TA268 to directly model second line therapy rather than indirectly by applying an adjustment to first line curves based on second line life years.

B8. Please provide the hazard ratios (with 95% confidence intervals) and the Kaplan-Meier curves of OS and PFS for the metastasis stage M1c subgroup population of the CA184-024, MDX010-08, and BRIM-3 trials.

B9. Please provide additional justification for the choice of cut-off point of two years for Kaplan-Meier data from the CA184-024 trial before fitting a parametric curve to the trial data up to five years.

a) Please explain the choice of cut-off point from a clinical point of view. Why would the hazard be expected to change at two years?

b) Please present cost-effectiveness results using alternative cut-off points to show the sensitivity of the results to changes in the switch point.

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B10. Please clarify that there are no relevant UK sources of registry data for long-term survival of advanced melanoma.

Quality of life

B11. Please clarify the reasons for assuming that health-related quality of life with vemurafenib is identical to ipilimumab at each time point before death (Table 44).

Adverse events

B12. Please confirm that the adverse event risk associated with ipilimumab for endocrine disorders is 0.4% (Table 39). The clinical study report for the CA184-024 trial suggests that this value is 2.8%.

Search strategy

B13. In section 10.10.4, page 259, an economics filter from the CRD website is mentioned. CRD has developed a search strategy for identifying economic studies however this does not appear to be the one that is used in the strategies presented. Please could the source of the economics filter used in the search strategies for MEDLINE, EMBASE and CINAHL be identified?

B14. The search strategies listed in section 10.13, pages 268-273, appear to be those relating to HRQL rather than strategies designed to capture cost studies or resource use studies. Have the correct search strategies been reported for this section?

B15. NHS HEED is reported as a database that was searched on pages 110, 151, and 161. Should this be NHSEED or HEED, or both, that were searched?

SECTION C: TEXTUAL CLARIFICATIONS AND ADDITIONAL POINTS

C1. On page 22, the number of patients in England and Wales who are expected to be diagnosed with advanced melanoma (stage IIIC-IV) and potentially eligible for treatment in 2014 does not take into account the 3.5% increase per year and is inconsistent with Table 81 on page 210; please clarify that the figure 1,190 reported on page 22 should read 1,319, consistent with Table 81.

C2. **PRIORITY QUESTION:** The NICE remit was “To appraise the clinical and cost effectiveness of ipilimumab within its licensed indication for previously untreated unresectable stage III or IV malignant melanoma”. However, the estimated number of patients eligible for treatment with ipilimumab described in section 8.1 (page 210) is calculated using the proportion of patients with stage IIIC or IV disease. Please clarify whether ipilimumab is also intended for use in patients with stage IIIA and IIIB disease, and, if so, estimate the number of patients eligible for treatment including these patients.

C3. In Figure 22, page 91, the number of subjects at risk is missing from the figure for the pooled dataset. Please provide these data.

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C4. **PRIORITY QUESTION:** Please define "duration of melanoma" in Table 12, page 50; does this relate to the time since diagnosis of the primary melanoma, or time since diagnosis of metastatic disease? In addition, on page 86, it states that "Duration of melanoma was higher in the pooled chemotherapy-naïve data set, presumably due to the fact that these patients may not be newly diagnosed." Please define what is meant by "newly diagnosed".

C5. The text at the bottom of page 95 appears to contradict that presented in Table 28, page 96. For example, in the text it states that the median time to resolution across all classes of immune-related AEs ranged from 1.4 to 4.7 weeks, however, in Table 28, the median time to resolution ranges from 2.0 to 4.7 weeks.

C6. The fourth paragraph of page 101 states that "Secondary analyses of 5-year data show an extended improvement in median OS of 24.5 weeks for ipilimumab 10 mg/kg + DTIC therapy vs. DTIC monotherapy". Should this read "Secondary analyses of 5-year data show an extended improvement in MEAN OS of 24.5 weeks for ipilimumab 10 mg/kg + DTIC therapy vs. DTIC monotherapy", consistent with the summary on page 100, and the fourth paragraph on page 65 (mean survival of 91.1 weeks compared with 66.6 weeks)?