

06 October 2011

NHS
**National Institute for
Health and Clinical Excellence**

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

Tel: 44 (0)20 7045 2246
Fax: (0)20 7061 9819
Email: bijal.joshi@nice.org.uk

www.nice.org.uk

Dear [REDACTED],

Re: Single Technology Appraisal – Ipilimumab for previously treated unresectable malignant melanoma

The Evidence Review Group (Liverpool Reviews and Implementation Group) and the technical team at NICE have now had an opportunity to take a look at the submission received on 20 June 2011 by Bristol-Myers Squibb Pharmaceuticals. 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 a written response to this letter to the Institute by **17:00, 26 July 2011**. 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.

We also request you to please provide the protocol, statistical analysis plan and clinical study report for the MDX01020 (Hodi 2010) and CA184-022 (Wolchok 2010) trials **as soon as possible**, preferably prior to collating a response to the clarification questions. If any of the responses to the clarifications questions can be found in the clinical study reports, clearly indicate in your response on which pages within the report this information can be found.

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.

If you have any further queries on the technical issues raised in this letter then please contact Richard Diaz – Technical Lead (richard.diaz@nice.org.uk) or Fiona Rinaldi – Technical Adviser (fiona.rinaldi@nice.org.uk). Any procedural questions should be addressed to Bijal Joshi – Project Manager (bijal.joshi@nice.org.uk) in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

- A1. **Priority Question:** Treatment discontinuation rates in the trial were high. Please provide the following information:
- Kaplan–Meier plot of the probability of discontinuation among patients assigned to all three arms
 - Updated overall survival analysis for patients who received all treatment schedules presented by treatment arm
 - Details of post discontinuation treatments received by patients in each of the three treatment arms
 - Information regarding whether any patients in the GP100 only arm received ipilimumab
- A2. The manufacturer's submission refers to protocol violations for eight treated patients. Please provide a report of all protocol violations that were identified during the study? These should be presented by the treatments arm
- A3. Page 86 of the manufacturer's submission states that all efficacy endpoints (except survival) in the MDX01020 trial were based on assessments made by a central independent review committee. However, the statistical analysis plan indicates that efficacy results are based on investigator-determined assessments. Please clarify which assessment procedures were planned, and which ones were actually used during the study?
- A4. Inclusion criteria for the pivotal trial stipulated that all patients had received previous systemic therapy. It is important in the appraisal to understand which prior treatments were given to patients. Please provide the number and percentages of the prior treatments by each treatment arm. Please also include the number of patients who had 1, 2, 3, and more than 3 previous systemic therapies.
- A5. The ERG notes that adverse event rates are high across all three arms of the pivotal trial. Please provide a rationale for the high adverse event rates in the gp100 only arm of the trial which is presented as being equivalent to best supportive care?

Section B: Clarification on cost-effectiveness data

- B1. **Priority Question:** Since the model results are critically dependent on the projected outcomes of the pivotal RCT (Hodi 2010), it is important for the ERG to have access to details of analyses of this data. Please provide product-limit survival tables (e.g. using SAS LIFETEST procedure or equivalent) from the analysis of the pivotal trial data by the 3 treatment arms (ipi only, ipi + gp100, gp100 only) for the following outputs (i.e. 3 outputs x 3 treatment arms = 9 K-M analyses):
- a) Progression-free survival b) Overall survival c) Post-progression survival

B2. **Priority Question:** Please provide product-limit survival tables (e.g. using SAS LIFETEST procedure or equivalent) from the analysis of the pivotal trial data (Hodi 2010) for overall survival :

- by 2 treatment arms (Ipi only & Ipi+gp100 combined, gp100 only)
- by 3 response groups – responders (CR/PR), stable disease (SD), progressive disease/others

(i.e. 3 response groups x 2 treatment arms = 6 K-M analyses)

For each of the above Kaplan-Meier analyses please provide a table of results showing the following for each event time:

- Time of each event (or time of censoring) from baseline (days)
- Product-limit estimate of survival proportion
- Standard error of survival proportion
- Number of patients failed (died/progressed)
- Number of patients remaining at risk

B3. **Priority Question:** The ERG wishes to explore the potential for predictive subgroups within the patient sample of the pivotal RCT (Hodi 2010). Please compare the characteristics of patients who are alive and uncensored for overall survival at 215 days after baseline, with patients who died or were censored for overall survival up to 214 days after baseline for each of the following baseline variables:

- mean age (t-test)
- proportion female
- proportion ECOG 0
- proportion M1c
- proportion Lactate dehydrogenase level > ULN
- proportion with CNS metastases
- proportion previously treated with Interleukin-2

Also please compare the above patients by:

- proportion with objective response recorded in the trial
- proportion with progression recorded before 215 days

The analysis should be carried out separately for gp100 only patients, and for all patients receiving Ipi (+/- gp100).

For each variable please provide the estimated central values with standard error, and a p-value for the difference between pre- and post-215 day survival patients.

- B4. **Priority Question:** The ERG wishes to assess the extent to which the comparator used in the manufacturer's model is representative of normal clinical practice, by comparing survival outcomes with similar patients treated in the UK and other European countries. Please provide product-limit survival tables for data from the MELODY study (Middleton 2010) for the following analyses:

Populations: a) UK patients;

b) non-UK patients

Included patients: Patients receiving a second-line systemic treatment

Excluded patients: a) Any patient receiving a second or subsequent line of treatment within a clinical trial

b) Any patient receiving immunotherapy at any time

Start of analysis: First day of second-line systemic treatment (Day zero)

Analyses requested: Overall survival from start of 2nd line systemic treatment for UK and non-UK populations separately

Please provide a table of results showing the following for each event time:

- Time of event (or censoring) from baseline (days)
- Product-limit estimate of survival proportion
- Standard error of survival proportion
- Number of patients failed (died/progressed)
- Number of patients remaining at risk

- B5. **Priority Question:** The ERG wishes to assess the extent to which the results are sensitive to gender balance within the patient population. Please provide values for an additional gender variable (M/F) for each of the two patient weight tables (A1:D56 and G1: J259) in the "Patient Weight Data" worksheet of the model.

- B6. **Priority Question:** Please provide patient BSA data matching tables in the "Patient Weight Data" worksheet including patient gender variables (M/F).

- B7. **Priority Question:** The ERG wishes to assess the relationship between recorded response, duration of response and overall survival in the pivotal RCT (Hodi 2010). Please provide a table containing the following information for each patient recorded as having a best overall response of complete response, partial response or stable disease:

- Treatment arm

- Best overall response
- Time (in days) from randomisation to first complete or partial response
- Time (in days) from randomisation to best overall response
- Time (in days) from randomisation to death/progression/censoring
- Event type when response time ends (death/progression/censored)