National Institute for Health and Clinical Excellence (NICE)
Midcity Place
71 High Holborn
London
WC1V 6NA

Dear Sir/Madam,

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 would like further clarification relating to the clinical and cost effectiveness data, as specified in the Clarification letter (**Questions A1-A5, Questions B1-B7**) received by the Bristol-Myers Squibb (BMS) on 12th July and an email about an **additional question** received by the BMS on 14th July.

The academic/commercial in confidence information is highlighted and underlined, that is, all information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

Section A: Clarification on effectiveness data

A1. Priority Question: Treatment discontinuation rates in the trial were high. Please provide the following information:

i. Kaplan–Meier plot of the probability of discontinuation among patients assigned to all three arms

[redacted]

Figure A1.1: [redacted]

[redacted]

Figure A1.2: [redacted]

iii. Details of post discontinuation treatments received by patients in each of the three treatment arms

[redacted]

[redacted]

[redacted]

[redacted]

Table A.1: [redacted]

Table A.1 (cont'd): [redacted]

Table A.1 (cont'd): [redacted]

[redacted]

iv. Information regarding whether any patients in the GP100 only arm received ipilimumab

[redacted]

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

[redacted]

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?

[redacted]

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.

[redacted]

[redacted]

Figure A4.1 [redacted]

[redacted]

Figure A4.2: [redacted]

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?

[redacted]

[redacted]

[redacted]

There are no approved drugs or accepted standard of care for patients with pretreated advanced melanoma and no treatment improves survival. The major treatment guidelines in the United States (US) (National Comprehensive Cancer Network, NCCN)[ii] and Europe (European Society of Medical Oncology, ESMO)[iii] recommend clinical trials for patient management.

Thus, absent any effective agent, the best choice for a control in a randomized trial is a well-studied investigational agent. The gp100 vaccine represents such a well-studied agent with moderate single-agent activity, the ability to enhance efficacy of interleukin-2 (IL-2), approved for untreated advanced melanoma in the US, in a randomized Phase 3 trial, and a well-characterized safety profile.[iv,v,vi,vii,viii,ix,x,xi,xii,xiii,xiv,xv,xvi,xvii,xviii,xix,xx]

In the history of prospectively randomized trials in advanced melanoma, there was only one study that met its primary efficacy endpoint (superiority). This study compared interleukin-2 (IL-2; approved for untreated advanced melanoma in the US)

plus a gp100 peptide vaccine with IL-2 alone and demonstrated a significantly improved response rate and progression-free survival (PFS) with a trend toward improved OS in favor of IL-2 plus gp100.[ix] This randomized Phase 3 study shows that the gp100 peptide vaccine is a well-studied and clinically active investigational agent and represents an appropriate therapeutic option in advanced melanoma where otherwise clinical trials are recommended for therapy. As such gp100 is adequate as a control and is favorable over other options such as best supportive care or placebo.

In the Phase 3 study MDX010-20, the addition of gp100 to ipilimumab did not negatively influence the survival outcome of ipilimumab.[xxi] Further, the survival in the gp100 control arm in MDX010-20 falls within the range of outcomes expected for this patient population and is consistent with the largest meta-analysis available.[xxii] Overall, this demonstrates that the comparison in MDX010-20 offers an interpretable result and that there is no harmful effect resulting from using gp100 as a control.

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

[redacted]

[redacted]

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

[redacted]

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.

[redacted]

Table B3.1 [redacted]

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

[redacted]

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.

[redacted]

Table B5

[redacted]

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

[redacted]

Table B6 [redacted]

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)

[redacted]

Additional Question: received on 14th July 2011

"The mean body surface area (BSA) used in the manufacturer's model (1.93 square metres) is inconsistent with all the other patient characteristics used as parameters in the model. In particular the mean body weight (78.83kg) used for costing ipilimumab is derived from the pivotal trial combined with the compassionate use programme. However, the BSA value incorporates data from a separate CLL trial of rituximab, and is clearly much larger than is compatible with the other data.

Please would the manufacturer provide the mean and standard deviation of BSA for patients in the Hodi trial, split between males and females, and the

mean and standard deviation of BSA for patients in the compassionate use programme also split between males and females"

[redacted]

[redacted]

[redacted]

[i] MDX010-20. A randomized, double-blind, multicenter study comparing MDX-010 monotherapy, MDX-010 in combination with a melanoma peptide vaccine, and melanoma vaccine monotherapy in HLA-A*201-positive patients with previously treated unresectable Stage III or IV melanoma; 2010. Bristol-Myers Squibb document control number 930041541.

[ii] Melanoma: Treatment Guidelines for Patients. Version IV, January 2008. American Cancer Society and National Comprehensive Cancer Network. Available at: http://www.rutlandskin.com/Melanoma%20guidelines%202008.pdf. Accessed on 17-Mar-2010.

[iii] Melanoma: Treatment Guidelines for Patients. Version IV, January 2008. American Cancer Society and National Comprehensive Cancer Network. Available at: http://www.rutlandskin.com/Melanoma%20guidelines%202008.pdf. Accessed on 17-Mar-2010.

[iv] Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: Moving beyond current vaccines. Nat Med. 2004; 10(9):909-915.

[v] Smith II JW, Walker EB, Fox BA, et al. Adjuvant immunization of HLA-A2-positive melanoma patients with a modified gp100 peptide induces peptide-specific CD8+ T-cell responses. J Clin Oncol. 2003 Apr 15;21(8):1562-1573.

[vi] Rosenberg SA, Yang, JC, Schwartzentruber DJ, et al. Impact of cytokine administration on the generation of antitumor reactivity in patients with metastatic melanoma receiving a peptide vaccine. J Immunol. 1999; 163:1690-1695.

[vii] Parkhurst MR, Salgaller ML, Southwood S, et al. Improved induction of melanoma reactive CTL with peptides from the melanoma antigen gp100 modified at HLA-A*0201-binding residues. J Immunol. 1996; 157(6):2539-2548.

[viii] Rosenberg SA, Yang JC, Schwartzentruber DJ, et al. Immunologic and therapeutic evaluation of a synthetic peptide vaccine for the treatment of patients with metastatic melanoma. Nat Med. 1998; 4(3):321-327.

[ix] Schwartzentruber DJ, Lawson D, Richards J, et al. A phase III multi-institutional randomized study of immunization with the gp100:209-217(210M) peptide followed by high-dose IL-2 compared with high-dose IL-2 alone in patients with metastatic melanoma. J Clin Oncol. 2009; 27:18s (suppl; abstr CRA9011).

[x] Walker EB, Miller W, Haley D, Floyd K, Curti B, Urba WJ. Characterization of the class I-restricted gp100 melanoma peptide-stimulated primary immune response in tumor-free vaccine-draining lymph nodes and peripheral blood. Clin Cancer Res. 2009 Apr 1;15(7):2541-51.

[xi] Walker EB, Haley D, Petrausch U, et al. Phenotype and functional characterization of long-term gp100-specific memory CD8+ T cells in disease-free melanoma patients before and after boosting immunization. Clin Cancer Res. 2008 Aug 15;14(16):5270-83.

[xii] Sosman JA, Carrillo C, Urba WJ, et al. Three phase II cytokine working group trials of gp100 (210M) peptide plus high-dose interleukin-2 in patients with HLA-A2-positive advanced melanoma. J Clin Oncol. 2008 May 10;26(14):2292-8.

[xiii] Meijer SL, Dols A, Jensen SM, et al. Induction of circulating tumor-reactive CD8+ T cells after vaccination of melanoma patients with the gp100 209-2M peptide. J Immunother. 2007 Jul-Aug;30(5):533-43.

[xiv] Di Pucchio T, Pilla L, Capone I, et al. Immunization of stage IV melanoma patients with Melan-A/MART-1 and gp100 peptides plus IFN-alpha results in the activation of specific CD8(+) T cells and monocyte/dendritic cell precursors. Cancer Res. 2006 May 1;66(9):4943-51.

[xv] Rosenberg SA, Sherry RM, Morton KE, et al. Altered CD8(+) T-cell responses when immunizing with multiepitope peptide vaccines. J Immunother. 2006 Mar-Apr;29(2):224-31.

[xvi] Roberts JD, Niedzwiecki D, Carson WE, et al. Phase 2 study of the g209-2M melanoma peptide vaccine and low-dose interleukin-2 in advanced melanoma: Cancer and Leukemia Group B 509901. J Immunother. 2006 Jan-Feb;29(1):95-101.

[xvii] Smith FO, Downey, SG, Klapper JA, et al. Treatment of metastatic melanoma using interleukin-2 alone or in conjunction with vaccines. Clin Cancer Res. 2008; 14:5610-5618.

[xviii] Stewart JH 4th, Rosenberg SA. Long-term survival of anti-tumor lymphocytes generated by vaccination of patients with melanoma with a peptide vaccine. J Immunother. 2000 Jul-Aug;23(4):401-4.

[xix] Lee KH, Wang E, Nielsen MB, et al. Increased vaccine-specific T cell frequency after peptide-based vaccination correlates with increased susceptibility to in vitro stimulation but does not lead to tumor regression. J Immunol. 1999 Dec 1;163(11):6292-300.

[xx] Salgaller ML, Marincola FM, Cormier JN, Rosenberg SA. Immunization against epitopes in the human melanoma antigen gp100 following patient immunization with synthetic peptides. Cancer Res. 1996 Oct 15;56(20):4749-4757.

[xxi] MDX010-20 clinical study report: a randomized, double-blind, multicenter study comparing MDX-010 monotherapy, MDX-010 in combination with a melanoma peptide vaccine, and melanoma vaccine monotherapy in HLA-A*0201-positive patients with previously treated unresectable Stage III or IV melanoma. May-2010. Bristol-Myers Squibb document control number 930043837.

[xxii] Korn EL, Liu P-Y, Lee S, et al. Meta-analysis of phase II cooperative group trials in metastatic Stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol. 2008;26:527-534.