NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab [ID760]

Dear [redacted],

The Evidence Review Group, Liverpool Reviews and Implementation Group (LR*i*G), and the technical team at NICE have now had an opportunity to take a look at the submission received on 23rd April 2015 by Merck Sharp & Dohme. 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 **10.00am on 4th June 2015** via NICE docs. 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 checklist for in confidence information available via NICE docs.

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 Pilar Pinilla-Dominguez, Technical Lead. Any procedural questions should be addressed to Bijal Joshi, Project Manager in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority question.** It is unclear why the crossover adjusted estimates of overall survival (OS) using the Rank-preserving structural failure time (RPSFT) method would fail to provide an accurate estimate of OS. Please provide a detailed justification of why the methods have been deemed to be unsuitable and why the results of the RPSFT analysis of KEYNOTE-002 OS have been rejected. Please also provide the code used to implement the RPSFT method and the full results of this analysis.

A2. **Priority question.** Please provide a full breakdown, for each method (RPSFT, 2-stage simple, 2-stage all covariates, Inverse probability of censoring weighted [IPCW]) of how in KEYNOTE-002 crossover adjusted estimates of OS were calculated.

a. Please clarify whether all patients who crossed over (to either dose of pembrolizumab) were adjusted for in the analyses, or whether it was only patients who crossed over to the pembrolizumab 2mg/kg arm.

b. If only patients who crossed over to 2mg/kg were adjusted for, how were the patients who crossed over to the pembrolizumab 10 mg arm considered?

A3. Table 21 of the company's submission presents KEYNOTE-002 progression free survival (PFS) rates at 3, 6, 9 and 12 months. Please provide hazard ratios and 95% confidence intervals for comparisons between pembrolizumab 2mg/kg and the control arm at each of these time points.

A4. For completeness, please provide the findings from the results of the first interim analyses conducted for KEYNOTE-002.

A5. Please provide the p-values for interaction for all performed subgroup analyses as presented in Appendix 7 of the company's submission for KEYNOTE-002 and KEYNOTE-001 (part B2).

A6. Please clarify which analysis population has been used for the KEYNOTE-001 (part B2) results presented in Table 32 of the company's submission.

Statistical methods employed in KEYNOTE-002:

A7. Please provide the level of power used for the sample size calculation for KEYNOTE-002.

A8. It is stated in the methods section for KEYNOTE-002 in the company's submission that "the OS hypothesis will be tested at 2.0%, 2.25% and 2.5% respectively if none,

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exactly one, or both hypotheses are rejected at the second interim analysis" referring to the two PFS hypotheses. If both PFS hypotheses are rejected at the second interim analysis at the 0.25% significance level as pre-specified for KEYNOTE 002, this would take up 0.5% of the overall pre-specified 2.5% alpha allocation, whereas if no PFS hypotheses are rejected at the second interim analysis, this would take up 0.0% of the alpha allocation. Should this sentence therefore read "the OS hypothesis will be tested at 2.5%, 2.25% and 2.0% respectively if none, exactly one, or both hypotheses are rejected at the second interim analysis"?

A9. Please clarify, why 95% CIs are provided for the PFS and OS results of KEYNOTE-002 at the second interim analysis when the level of testing is 0.5% for OS and 0.25% for PFS? These confidence intervals could be misinterpreted as significant results, whereas the significance depends on the p-value for the test.

A10. For PFS, results are reported for both Central Assessment (IRO) and Investigator Assessment (INV) of disease progression. It is not clear why the company claims to have controlled the type 1 error strictly yet performed multiple analyses, seemingly without making adjustments for multiplicity. Please clarify if there were any adjustments for multiplicity.

A11. For KEYNOTE-002, it is pre-specified that the full-analysis set population will be used for the analysis of objective response rate (see Table 11), but results for the intention-to-treat (ITT) population are presented. Please provide justification for this choice.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** The ERG have detected indications in the KEYNOTE-002 data used in the model that informative censoring at data cut-off may be exaggerating hazards in both trial groups, and wish to examine the extent to which this may be introducing bias and additional uncertainty into the model results. Please provide the following Kaplan-Meier analyses (listed in a to h below) to the following specification:

Population: Use the ITT population including all patients lost to follow-up or withdrawing from trial.

Censoring: Censor lost to follow-up and withdrawn patients at the time recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, and not when last seen. Please use the format of the table provided below.

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Trial data set: Keynote-002, latest data cut.

a. Time to death from any cause (OS) Kaplan-Meier analysis for the pembrolizumab 2mg/kg treatment group.

b. Time to death from any cause (OS) Kaplan-Meier analysis for the comparator treatment group, without adjustment for crossover, stratified by those who did and those who did not crossover following disease progression.

c. Time to death from any cause (OS) Kaplan-Meier analysis for the comparator treatment group, separately for each method of crossover adjustment (RPSFT, 2-stage simple, 2-stage all covariates, IPCW).

d. Time to disease progression or death (PFS) Kaplan-Meier analysis based on investigator assessment, stratified by treatment group.

e. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis for the pembrolizumab 2mg/kg treatment group.

f. Time from disease progression by investigator assessment to death from any cause (post-progression survival [PPS]) Kaplan-Meier analysis for the comparator group, without adjustment for crossover, stratified by those who did and those who did not crossover following disease progression.

g. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis for the comparator group, separately for each method of crossover adjustment (RPSFT, 2-stage simple, 2-stage all covariates, IPCW).

h. Time to treatment discontinuation Kaplan-Meier analysis.

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Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

B2. **Priority question:** The use of secondary data sources for projection of short-term differences in survival to long-term gains requires compatibility between the trial and the secondary sources, in terms of those patient characteristics known to influence survival. In particular, the duration of diagnosed melanoma at baseline in the trial is important in assessing the validity of the manner in which secondary data sources are used to project survival beyond the trial period. Please provide a table summarising the baseline characteristics as shown in Table 16 of the company's submission, together with the time since initial diagnosis of malignant melanoma (mean and range) of patients in the KEYNOTE-002 trial for the 3 subgroups: 'pembrolizumab treated (2mg/kg)', 'comparator treated without crossover', 'comparator treated with crossover'.

B3. **Priority question:** The ERG wishes to assess whether there is clinical and analytical evidence of heterogeneity in the KEYNOTE-002 as it may prove important in establishing the appropriateness of the methods used to project survival in the model. Please provide a table summarising the same baseline characteristics of patients in the KEYNOTE-002 trial as in B2, but splitting each subgroup into 2 approximately equal sections (patients who progressed or died early versus patients who progressed or died later or who remained alive and progression-free at the time of data cut, that is a 50/50 split).

B4. **Priority question:** The company's model assumes that all patients enter the trial at a fixed age, and with fixed proportions of males and females. A detailed age/sex

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breakdown would allow the ERG to assess the magnitude of any bias introduced by this effect. Please provide a table showing the baseline age-sex distribution of patients in the KEYNOTE-002 trial in 5 year age bands (under 20, 20-24,25-29,etc.), for patients in the pembrolizumab 2mg/kg treated arm, and separately for comparator treated patients who did or who did not crossover on disease progression.

B5. **Priority question:** Although the KEYNOTE-002 utility results have been calculated using the UK tariff of social values, a substantial proportion of EQ-5D responders are from US residents. The ERG considers it important to consider any uncertainty introduced into the cost-effectiveness results from including data from US responders. Please provide results for EQ-5D scores in the KEYNOTE-002 trial split between US and non-US patients for Appendix 20 Tables 3, 5, 7 and 9.

B6. Neither the company's submission nor the submitted model state which definition of assessment was selected when analysing KEYNOTE-002 trial data for inclusion in the model. Please clarify whether model PFS projections are based on IRO or INV of disease progression.

B7. Please explain why on page 155 you consider the two-stage crossover model which included all the covariates to be the most conservative.

B8. Please clarify the following inconsistency. On page 32 of the company's submission, it is claimed that "Therefore, pembrolizumab is expected to displace the use of BSC (including dacarbazine) to further subsequent lines of treatment for patients experiencing disease progression" and on page 136 it is restated that "it is expected that pembrolizumab would be used prior to chemotherapy treatment where possible". However your economic model did not include post progression therapy (including dacarbazine) after progression with pembrolizumab. Clinical advice to the ERG also suggested that there might be situations where clinicians may also prefer to use BRAF inhibitors after treatment with pembrolizumab, as opposed to prior to this. Therefore, please clarify whether Figure 3 in the company's submission may need adapting and these 2 scenarios considered.

Section C: Textual clarifications, references and additional points

C1. The ERG appreciates the company providing the clinical study reports for KEYNOTE-002 and KEYNOTE-001 (part B2) which include the statistical analysis plans. In addition, please provide the study protocols for these 2 trials.

C2. The ERG notes that although not statistically significant, compared with patients receiving 2mg/kg, OS appears to be improved in patients receiving 10mg/kg in both KEYNOTE-001 (part B2) and KEYNOTE-002 whereas response rates in KEYNOTE-001 (part B1) also appear to be improved with the higher dose (particularly when administered fortnightly). Please provide more context as to why the 2mg/kg dose is preferred over the 10mg/kg dose.

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C3. Please provide a reference (and if not already provided, accompanying document) for the methods used to control the overall type 1 error rate in KEYNOTE-002 (as mentioned on pages 57 to 58 of the company's submission.

C4. The number of patients estimated to be eligible for treatment with pembrolizumab by the company is cited to be 628. However, following the text and tables in section 6.2 of the company's submission, the ERG has been unable to replicate these numbers. Specifically, from following the text in section 6.2 and numbers cited in Tables 94 to 96 of the company's submission, the ERG calculates the numbers as follows:

Parameters	Proportion	Source	Number
Total population - England		Table 94: ONS Mid-2013 UK population estimates	53,865,800
Estimate of incident melanoma population	0.02%	Table 94: Calculated (average of male and female) from ONS cancer registration 2012 (released June 2014	11,366
Proportion of patient with stage IIIc or IV disease	10.00%	Table 94: Vemurafenib NICE costing report (NICE costing template TA269)	1,137
Proportion of patients who are $BRAF^{V600}$ mutation-positive	48.00%	Table 94: Long et al	546
Proportion of patients who are $BRAF^{V600}$ mutation-negative	52.00%	Table 94	591
Patients who are $BRAF^{V600}$ mutation-positive			
- Treated first line with BRAF inhibitor and/or MEK inhibitor	43.20%	Table 95	236
- Treated first line with ipilimumab	16.30%	Table 95	89
- Treated second-line following treatment with BRAF inhibitor and/or MEK inhibitor*	65.00%	Table 95: Merck Sharp & Dohme. Data on file. 2015. Ref Type: Data File (Table 95)	153
- Treated second-line following treatment with ipilimumab*	75.00%	Table 95: Merck Sharp & Dohme. Data on file. 2015. Ref Type: Data File (Table 95)	67
Patients who are $BRAF^{V600}$ mutation-negative			
- Treated first line with ipilimumab	75.00%	Table 96	443
- Treated second-line following treatment with ipilimumab*	75.00%	Table 96: Merck Sharp & Dohme. Data on file. 2015. Ref Type: Data File (Table 96)	332
All patients treated second-line			
Patients eligible for treatment with pembrolizumab		Calculated (sum of $BRAF^{V600}$ mutation positive + $BRAF^{V600}$ mutation negative)	552

* The proportion of patients treated first-line minus those who withdrew treatment as a result of death, performance status, contraindication or adverse event.

Please clarify how the estimate of 628 patients is derived, noting if any errors have occurred in the ERG's calculations above. In particular, the ERG queries whether the proportion of patients who are $BRAF^{V600}$ mutation-positive and

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treated first line with ipilimumab (16.3% as reported in Table 95) may be an underestimate?

C5. Please clarify if the source for all data reported in Table 95 is reference 88: Merck Sharp & Dohme. Data on file. 2015. Please also provide a copy of this document.

C6. Please clarify if the source for all data reported in Table 96 is reference 88: Merck Sharp & Dohme. Data on file. 2015.

C7. Please clarify whether in Table 96, "% treated with BRAFi* +/- MEKi in 1L" should in fact read "% treated with ipilimumab in 1L".

C8. One key exclusion criterion for entry into KEYNOTE-002 is listed on page 46 of the company's submission as "Disease progression within 24 weeks of last dose of ipilimumab." However "Disease progression within 24 weeks of last dose of ipilimumab" is also used to define a patient who is refractory, a key inclusion criterion (page 43 of the company's submission). Please clarify whether "Disease progression within 24 weeks of last dose of ipilimumab" is an inclusion or exclusion criterion.