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Single Technology Appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Dear [redacted]

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRiG), and the technical team at NICE have now had an opportunity to take a look at the submission received on 6th November 2015 by Amgen. 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.

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

Please provide your written response to the clarification questions by **5pm** on **10th December 2015**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals **https://appraisals.nice.org.uk/request/9531**.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information 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.

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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 [redacted]

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Korn adjustments conducted in order to provide evidence for clinical effectiveness:

A1. **Priority question.** Please provide full details of the modified Korn and two-step Korn analyses conducted with references cited (and the accompanying relevant documents provided) and full details of calculations conducted (including how coefficients were derived), ideally in Microsoft Excel format.

A2. **Priority question.** In relation to tables 4-24 to 4-26:

a. Please clarify that the data entered for patients with no visceral disease for patients previously untreated with ipilimumab in Table 4.24 is 0.17 and not 17 as stated

b. The formula for estimating the hazard ratio (HR) for T-VEC in Table 4-26 appears to be incomplete. Please clarify whether this is the case and if so, provide the correct formula

c. For Table 4-24, please provide further details on the methodology used to derive the overall survival (OS) estimate for the monotherapy ipilimumab 3mg/kg group, as used in the company's submission in the NICE technology appraisal of ipilimumab for previously untreated (unresectable or metastatic) melanoma (TA319), using data from the trial of ipilimumab + dacarbazine.

d. In Table 4.25, there is reference to the weighted average of HRs for patients with stage M0 and M1a melanoma reported in Robert 2011. Please clarify how this weighted average was calculated and provide any relevant references for the method used.

A3. **Priority question.** For Figures 4.12 to 4.16, please provide a table providing the median and mean survival estimates (i.e. OS or progression-free survival [PFS], depending on the figure) for all presented curves in each figure.

A4. **Priority question.** The company's submission does not include a figure accounting for the 95% prediction intervals around the OS estimates. Please provide a new figure with 95% prediction intervals around the two-step Korn adjusted OS estimate for ipilimumab (and a corresponding table with median and mean OS estimates, as described in **Error! Reference source not found.** above).

A5. **Priority question.** Please clarify whether data from OPTiM used for the Korn adjustments for PFS is time to treatment failure (TTF) data.

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A6. **Priority question.** Please provide further clarification on why the Hodi 2014 study, which compares ipilimumab monotherapy with ipilimumab + GM-CSF was excluded from the company's analyses using the Korn algorithm. The reason cited for the exclusion of this study (in the appendices to the company's submission) is that it does not include a relevant comparator. However, in the company's analyses, the company has used gp100 and dacarbazine as comparators. Please clarify why gp100 and dacarbazine are considered to be relevant comparators but ipilimumab + GM-CSF is not.

A7. **Priority question.** Please justify why it is appropriate to pool data from both the ipilimumab monotherapy and ipilimumab + dacarbazine arms, and from trials of both previously treated and previously untreated patients. Please clarify whether the heterogeneity that may arise from these differences in the trials was considered/assessed and if so, how.

A8. **Priority question.** Please clarify why the company did not include, in its analyses using the Korn algorithm data, from the CheckMate 067 and KEYNOTE 006 trials. If possible, please provide Korn adjusted OS and PFS estimates for ipilimumab (using both the modified and two-step methods) based on analyses that include data from the CheckMate 067 and KEYNOTE 006 trials.

OPTiM trial:

A9. Table 4-5 implies that response onset was assessed by investigator only. Table 4-17 provides data for "time to response per Endpoint Assessment Committee (EAC)". Please clarify if response onset was assessed by EAC.

A10. On page 59, it is stated that "The null hypothesis was that there is no difference in durable response rate (DRR) between T-VEC and control at interim or final analysis." Please clarify whether the null hypothesis should actually refer to the primary analysis of DRR, rather than the interim or final analysis of DRR.

A11. Primary and secondary outcomes are reported at both the primary and final data-cuts. Please clarify whether it was pre-specified that these outcomes would be reported at both the primary and final data-cuts.

A12. Please clarify the level of significance testing used for the analysis of DRR at the final data-cut as this final analysis is not mentioned in the Bonferroni alpha allocation described in the statistical analysis plan (SAP).

A13. Please clarify which subgroup analyses were pre-planned for both DRR and OS analyses as they are not specified in the SAP or in the protocol. Please also provide the results for the tests of treatment interactions for the planned subgroup analyses.

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A14. Table 4-18 provides an analysis for TTF for patients with stage IIIB-IVM1a disease at the time of the primary data-cut. If available, please also provide this analysis for the final data-cut.

A15. Based on Figure 4-4 it appears that significantly more patients randomised to GM-CSF than to T-VEC withdrew from the study without having received any of the assigned treatment ([4/295] 1.4% T-VEC vs [14/141] 9.9% GM-CSF):

a. if possible, please provide a similar patient disposition flow diagram to Figure 4-4 only including patients with non-visceral disease (at least for those who were randomly assigned treatment since such data are unlikely to be available for those not randomised)

b. if a flow diagram is not possible, please indicate how many of the early withdrawals in each trial arm were from the non-visceral subgroup.

A16. Table 4-7 provides data on the number of patients who withdrew from study treatment in the intention-to-treat (ITT) population and non-visceral subgroup. Please provide a summary of the reasons for (i) discontinuing treatment and (ii) discontinuing from the trial in each study arm in the non-visceral subgroup.

A17. It is unclear whether the data for subsequent therapies reported in Table 4-10 are correct. Specifically, please clarify:

a. that the data reported in the top row of Table 4-10 (i.e. ipilimumab, vemurafenib, dabrafenib, trametinib or anti-PD1 antibody) are a summation of all the data in the rows below

b. that data in the rows below are mutually exclusive (and hence should not necessarily equal the data reported in the top row)

c. that the correct data have been input since the data reported for the ITT population do not appear to match the data reported in Table 14-8.1.7 of the clinical study report (CSR) and for the T-VEC group, a greater number of patients are reported to have received ipilimumab, dabrafenib and trametinib in the population in whom T-VEC is indicated (that is, non-visceral disease) than in the whole ITT population.

A18. In relation to A17.b, please clarify that where it is stated that “DR was associated with reduced risk of initiating subsequent systemic therapy” (company’s submission, page 67), this analysis has been conducted with the correct data set for subsequent systemic therapy.

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Section B: Clarification on cost-effectiveness data

N.B. When referring to PFS data below, the ERG is referring to the data labelled PFS in the company's economic model.

Kaplan-Meier analyses for OPTiM trial:

B1. **Priority question:** The ERG has detected that the time-to-event results from the OPTiM trial are subject to substantial right-censoring especially in the T-VEC group and suspects that 'informative censoring' might have been introduced and therefore, the results poorly reflect the true profile of time-to-event hazards. The ERG wishes to investigate the extent to which this may be introducing bias and additional uncertainty into the model results. In addition, neither the published trial results nor the company's submission includes Kaplan-Meier results for PFS or Post-Progression Survival (PPS), so it is not possible for the ERG to verify that the partitioning of OS into PFS and PPS components is accurately reflected in the company's model.

Please provide the following Kaplan-Meier analyses (a, b and c below), to the following specification (using the final data-cut from OPTiM):

Population: OPTiM clinical trial non-visceral subgroup (stage IIIB/C and M1a) including all subgroup patients lost to follow-up or withdrawing from trial.

Censoring: Censor lost to follow-up and withdrawn patients at the date 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; i.e. not when last known to be alive (OS and PPS), and not at the date of last tumour assessment (PFS).

Analyses:

a. Time to death from any cause (OS), stratified by treatment group (T-VEC vs GM-CSF) and stage of the disease (IIIB, IIIC and M1a).

b. Time to disease progression or death based on investigator assessment (PFS), stratified by treatment group (T-VEC vs GM-CSF) and stage of the disease (IIIB, IIIC and M1a).

c. Time from disease progression to death from any cause (PPS), stratified by treatment group (T-VEC vs GM-CSF) and stage of the disease (IIIB, IIIC and M1a).

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Please present analysis outputs using the following format:

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

Korn adjustments conducted in order to provide evidence for cost effectiveness:

B2. **Priority question: Application of Korn adjustments:** Figures 5-30 and 5-32 indicate that in the T-VEC group the PFS estimates (and hence also the PPS estimates) are altered by the Korn adjustments, whereas OS is unaffected when either of the Korn adjustments are applied to the model. The ERG considers this to be incorrect because the role of the Korn adjustments should only be to generate OS and PFS estimates for the comparators from the pooled data for ipilimumab and therefore, the OPTiM trial-based information should not be affected. Please clarify how the company considers the model should be amended to remove this error, indicating how the reported model results are altered.

B3. **Priority question: Korn adjusted ipilimumab OS and PFS estimates:** The ERG wishes to validate the accuracy of the figures on which the cost-effectiveness estimates are based. Please provide Kaplan-Meier estimates for OS and PFS before and after Korn adjustments in the same format as indicated above for **Error! Reference source not found.**.

OPTiM trial data required for cost-effectiveness analyses:

B4. **Priority question:** Time from diagnosis: Please provide the mean, standard deviation and standard error of the mean for the time from initial diagnosis to date of randomisation for each treatment group of the OPTiM clinical trial.

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B5. T-VEC treatment – first cycle: Please provide the number of patients randomised to T-VEC who required 0, 1, 2, 3, … vials for their first treatment in the OPTiM trial.

B6. T-VEC treatment – subsequent cycles: Please complete the following table for all subsequent treatment cycles with T-VEC in the OPTiM trial:

Treatment cycle	Patients still on treatment	Total vials used in cycle
2	n_2	v_2
3	n_3	v_3
4	n_4	v_4
5	n_5	v_5
6	n_6	v_6
…	…	…

B7. Body weight: Please provide the mean and standard deviation of body weight separately for males and females randomised to treatment with T-VEC in the OPTiM trial.

Section C: Textual clarifications, references and additional points

C1. **Priority question.** Please provide a published paper describing the modified Korn method. The company notes this was used in the appraisal of ipilimumab for previously untreated (unresectable or metastatic) melanoma (TA319) but the only reference that appears to be cited in TA319 (Bristol-Myers Squibb Company. Meta-analysis of overall survival from literature publications and study MDX010-20) is unavailable to the ERG.

C2. Figure 3-1 includes a treatment pathway option for patients with BRAF V600 mutation positive disease starting with pembrolizumab followed by ipilimumab as a second-line option which is absent from Figure 3-2. Please clarify whether the company believes a treatment pathway starting with pembrolizumab and followed by T-VEC for patients with BRAF V600 mutation positive disease would be appropriate.

C3. Figure 4-2 (PRISMA flow diagram for non-RCT evidence) seems to be identical to Figure 4-1 (PRISMA flow diagram for RCT evidence). Please provide the correct figure for Figure 4-2.