NICE National Institute for Health and Care Excellence

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Single technology appraisal

Trametinib in combination with dabrafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID661]

Dear Antonia,

The Evidence Review Group, Liverpool Reviews and Implementation Group, and the technical team at NICE have looked at the submission received on 1st December 2015 from Novartis Pharmaceuticals. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

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 21st January 2016.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK on 'NICE Docs/Appraisals'].

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 as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

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

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted]. Any procedural questions should be addressed to [redacted]

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. In the company submission, the results for the subgroup analyses are presented in figures 19 and 20 for the COMBI-d trial and figures 21 and 22 for the COMBI-v trial. Please provide the p values for the tests for interaction for all subgroup analyses for overall survival (OS) and progression-free survival (PFS).

A2. On page 127 (section 4.8.2) of the company submission, a list of planned exploratory subgroup analyses is presented. This list includes a subgroup analysis according to 'prior immunotherapy (yes or no)'. Please provide the OS and PFS results for the subgroups of patients in the COMBI-d trial who did, and did not, receive prior immunotherapy treatment.

A3. Across all the trials reported in the company submission, the Pike estimator is used to conduct the stratified log-rank test for PFS and OS. Please explain why the Pike estimator was chosen in preference to the Cox proportional hazards model.

A4. The Reporting and Analysis Plan (RAP) provided in the company submission for the COMBI-v trial is stated to be the latest version (amendment number 4). It is not clear when the first version of the RAP was finalised, or what changes have been made between version 1 and version 4. Please provide either the first version of the RAP or a RAP revision history table, so that comparisons can be made between the first and the current version.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Revised Kaplan-Meier (K-M) analyses

Please provide the K-M analyses detailed in points 1a, 1b, 2a and 2b for the ITT populations including all patients who were lost to follow-up, or who withdrew from the trials. Please censor patients lost to follow-up, and those who withdrew from the trials 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, not at the point when last known to be alive (for OS and post-progression survival [PPS]), or at the date of the last tumour assessment (for PFS).

1. **Trial data set**: COMB-d; 12th January 2015 data cut (if available, otherwise the most recent data):

    a. Time to death from any cause (OS), time to disease progression or death based on investigator assessment (investigator-assessed PFS), and time

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from disease progression by investigator assessment to death from any cause (PPS), stratified by treatment arm (trametinib plus dabrafenib compared with dabrafenib).

b. Time to treatment discontinuation, stratified by treatment arm (trametinib plus dabrafenib compared with dabrafenib).

2. **Trial data set**: COMB-v; un-crossed data, 13th March 2015 data cut (if available, otherwise the most recent data):

   a. Time to death from any cause (OS), time to disease progression or death based on investigator assessment (investigator-assessed PFS), and time from disease progression by investigator assessment to death from any cause (PPS), stratified by treatment arm (trametinib plus dabrafenib compared with vemurafenib).

   c. Time to treatment discontinuation, stratified by treatment arm (trametinib plus dabrafenib compared with vemurafenib).

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

B2. **Priority question:** Please provide results for EQ-5D utility scores (using UK valuation) in the COMI-d and COMBI-v trials (January 2015 and March 2015 data cut if available, otherwise the most recent data), showing (i) the number of valid patient responses (at baseline and every 8 weeks thereafter through to week 56, and then

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every 12 weeks until progression, at progression and 5 weeks post-progression), and (ii) the mean and standard deviation of the EQ-5D values every time these data were recorded, stratified by treatment (COMBI-d: trametinib plus dabrafenib compared with dabrafenib; COMBI-v: trametinib plus dabrafenib compared with vemurafenib).

B3. **Priority question:** Please repeat the analyses in question B2, for each of the 3 subgroups defined by country of origin:

a. USA and Canada

b. Europe

c. Other

B4. **Priority question:** Using the latest available data from the COMBI-d and COMBI-v trials, and omitting any patient who switched treatment, please provide a table for each trial showing the number of patients in each treatment arm who continued to receive their assigned study treatment after disease progression. Please also include the median time between progression and treatment discontinuation for these patients.

B5. Please clarify whether patients in the COMBI-d and COMBI-v trials, whose disease had progressed but who remained on study treatment, were categorised as having had disease progression in all analyses undertaken after the point at which progression was identified.

B6. Please provide details of the criteria that were used to stop treatment in patients whose disease had progressed but who remained on study treatment.