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National Institute for Health and Clinical Excellence

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[redacted]

Re: Single Technology Appraisal – Vemurafenib for the treatment of locally advanced or metastatic, BRAFV600 mutation positive malignant melanoma

The Evidence Review Group (Liverpool Reviews & Implementation Group) and the technical team at NICE have now had an opportunity to look at your responses to the ERG's clarification questions received on the 9th March 2012. The ERG understands that you are unable to provide the October 2011 cut off data to Priority requests C1 and C3. The ERG considers it important that similar data should be considered in their report and therefore request that these analyses be completed using the March 2011 cut-off of the BRIM3 trial data. The ERG would be happy to clarify any points of uncertainty relating to the supplementary requests below.

We request you to provide a written response to this letter to the Institute as soon as possible, but no later than 22nd March 2012. 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 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.

[redacted]

Yours sincerely

[redacted]

Encl. checklist for in confidence information

Supplementary Requests

The ERG believes the presented clinical results do not allow for exploration of issues related to time-to-events. Therefore, the ERG would like to request the following additional results in the format of Product-Limit Survival tables (that is, using SAS LIFETEST procedure, an example is included at the end of this document) showing for each event time:

- Time-to-event from baseline (days)
- Product-limit estimate of survival proportion
- Standard error of survival proportion
- Number of patients failed
- Number of patients remaining at risk

Please provide full Product-Limit Survival tables as follows:

A1. For patients receiving at least 1 dose of randomised treatment, who subsequently had a non-fatal disease progression event recorded (i.e. survived at least 1 day after the date of disease progression), please provide the following:

- A progression free survival from the March 2011 cut of the BRIM3 trial data by trial arms (vemurafenib and dacarbazine).

- Post-progression survival from the date of non-fatal disease progression by trial arms (vemurafenib and dacarbazine), with dacarbazine patients data censored at the date of cross-over to vemurafenib, using the March 2011 cut of the BRIM3 trial data.

A2. For patients receiving at least 1 dose of vemurafenib treatment, please provide the following:

- Define two mutually exclusive subgroups of patients: those who continued on vemurafenib treatment until disease progression, death or censoring for data cut-off; those who discontinued vemurafenib treatment prior to disease progression, death or censoring for data cut-off.

- Based on the above definitions, please carry out a Kaplan-Meier analysis comparing these two subgroups in terms of progression free survival and overall survival using the March 2011 cut of the BRIM3 trial data.

Example of output (SAS) required from analyses specified in C1

The LIFETEST Procedure

Product-Limit Survival Estimates						
SURVIVAL		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...		0.8548	0.1452	0.0447	9	53
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