National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation positive malignant melanoma

Below is the table outlining the LRiG comments related to the factual error check provided for this STA
### Issue 1  Page 53

<table>
<thead>
<tr>
<th>Description of problem</th>
<th>Description of proposed amendment</th>
<th>Justification for amendment</th>
<th>LRiG response</th>
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<tbody>
<tr>
<td>In the first paragraph of page 53 it is stated:</td>
<td>This statement should be removed.</td>
<td>Vemurafenib has been demonstrated to improve overall survival (BRIM3). Therefore crossover from dacarbazine to vemurafenib will inevitably result in improved survival outcomes for patients who crossover. As discussed on page 159 to 162 of the manufacturer’s submission, and as demonstrated in figures 38 and 39 of our submission (reproduced in the appendix below for ease of reference) the risk of death for a patient randomised to dacarbazine dropped by nearly 20% between the March and October data cuts. This reduction coincided with an increase in the rate of crossover to 24% of patients randomised to dacarbazine. Aside from the impact of crossover nothing changed between these two cuts of data. The fact that the risk of death for patients randomised to dacarbazine appears largely unchanged for the first four months of the survival curves (when patients randomised to dacarbazine would still be expected to be receiving dacarbazine) but then reduced from month 4 onwards (when crossover would be expected to begin taking place) indicates strongly that this reduction is due to the impact of crossover.</td>
<td>The ERG do not consider this a factual error. They have simply suggested an interpretation of the data submitted by the manufacturer. No changes have been made to the document</td>
</tr>
<tr>
<td>‘suggests that ..... crossover of patients from dacarbazine to vemurafenib has no effect on OS’. This is factually inaccurate as substantial evidence has been submitted by the manufacturer that demonstrates crossover has a major effect on overall survival.</td>
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**Conclusion:**
It is logical that crossover to an effective treatment would result in a reduction in the risk of death and confounding of incremental survival analysis. Such a reduction was observed in BRIM3. We therefore believe the statement that ‘crossover of patients from dacarbazine to vemurafenib has no effect on OS’ is factually inaccurate and should be removed from the report.

### Issue 2  Pages 51-53

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| On pages 51-53 of the report the ERG suggest that after 97 days of treatment with vemurafenib it 'no longer provides any survival benefit compared with dacarbazine'. This is factually inaccurate and inconsistent with the evidence available. | This statement should be removed or amended appropriately to reflect the following facts contained within the manufacturer’s submission:  
- Figure 7 (page 52 of the ERG report), upon which the 97 days estimate is based, is confounded by crossover  
- the BRIM2 ‘swim-plots’ demonstrate that response to vemurafenib is | 1. In Figure 6 it is clear that the risk of death in the vemurafenib arm continues to be lower than that in the dacarbazine arm beyond day 97 (i.e. the slope of the cumulative hazard for vemurafenib is lower than that for dacarbazine). The suggestion that these two curves are parallel (indicating that the risk of death is constant between the two) is factually inaccurate. On page 159 of our submission we detail an analysis considering solely the ‘stabilized’ hazard period of the March data-cut and show that in this period, whilst reduced, the treatment effect associated with vemurafenib is still positive (with an OS HR of | Again – the ERG do not consider this a factual error. This is simply the ERG’s preferred interpretation of the data.  
No changes have been made to the document |
typically far longer than 97 days

- In Figure 6 the two cumulative hazard plots continue to diverge from day 97 onwards (as shown in Figure 35 of our submission (page 157)).

approximately 0.89 from month 4 onwards) – Reproduced in the appendix below for ease of reference.

2. The ERG’s assumption that the effect of vemurafenib is limited to 97 days is in direct conflict with the ‘swim-lane’ plot available from the BRIM2 study (Figure 20 in the submission – reproduced in the appendix below for ease of reference). This plot demonstrates that response to vemurafenib is maintained far beyond 97 days for the vast majority of patients (and up to 20 months in some patients). As mortality is strongly linked to tumour growth it is factually inaccurate to suggest that the effect of vemurafenib is limited to 97 days. Whilst it is inevitable that at some point vemurafenib will no longer be effective in suppressing a tumour, the ERG’s assumption that no patient gains further benefit beyond 97 days of treatment appears erroneous in light of the evidence submitted.

3. The use of Figure 7 to support the assumption that vemurafenib provides no further treatment effect beyond day 97 is flawed as this data is heavily confounded by crossover (as noted in ‘Issue 1’ above). Due to crossover the risk of death in the dacarbazine arm dropped by approximately 20% between these two data cuts and so it is inevitable that the relative effect of vemurafenib and dacarbazine (with...
24% of patients crossing over to vemurafenib upon progression) will be reduced in this later cut. The suggestion that the treatment effect is limited to 97 days based upon Figure 7 without full consideration of the impact of crossover omits important factual information.

**Conclusion:**
This section of the ERG report omits important evidence on the durability of response to vemurafenib as observed in the BRIM2 study and the impact of crossover on the BRIM3 October cut. Furthermore it includes the statement that the hazard profiles of patients receiving vemurafenib and dacarbazine are equivalent from day 97 onwards. This is factually inaccurate as the hazard plots are not parallel in the data less confounded by crossover (the March cut – Figure 6).

### Issue 3  Page 7

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<tr>
<td>In the first paragraph of page 7 it is stated that ‘Data from this second trial (BRIM2) was not considered robust by the manufacturer’. This is factually inaccurate. We believe this data is</td>
<td>This paragraph should be amended to reflect the fact that BRIM2 was a robust study conducted to high standards, but that due to its single arm design it is not possible to conduct a robust cost-utility analysis utilising</td>
<td>This statement suggests Roche believe a well-conducted study published in the New England Journal of Medicine is not robust. This is not the case and requires amendment.</td>
<td>The ERG agrees that the wording is somewhat mislead ing The quote from the MS regarding the robustness of the evidence has been inserted in the report</td>
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not sufficient for undertaking a cost-utility analysis but is ‘robust’ in terms of what the study was designed to do.

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<td>In the first paragraph it is stated that the distributions used in PSA have not been provided. These were provided in Table 32 of our submission from page 182 onwards.</td>
<td>This should be amended to reflect the fact that this information was provided.</td>
<td>This statement is factually inaccurate.</td>
<td>The statement is an error. The structure of the MS led to this error. The table is in section 6.3.6 and is not referred to in the text of the document while the PSA is discussed in section 6.5.3. The report has been amended. Page 46</td>
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</table>
Appendix

Issue 1 – Crossover reduced the risk of death in the dacarbazine arm by nearly 20% between the two data-cuts.

Figure 1: BRIM3/Robert dacarbazine OS KM curves (March cut)

Note that the slope in Figure 39 is equal to that of Figure 38 up to month 4 at which point the risk of death in the October cut reduces.
This is highly suggestive of the influence of crossover.

**Issue 2** – The assumption that the treatment effect associated with vemurafenib in limited to 97 days is factually incorrect.

**Figure 3:** BRIM2 Time to response and time of progression by individual patients who responded to treatment (n = 69).

Note that the ERG’s assumption that the effect of vemurafenib is limited to 97 days is counter to the evidence available from BRIM2.
Note: the ratio of the two slopes above is the hazard ratio. This figure demonstrates that whilst the hazard ratio is lowest for the first 4 months of the study it is still below 1 from month 4 onwards (approximately 0.89). In the base-case modelling this treatment effect was conservatively limited to 14 months but could feasibly be longer. The ERG in effect assume that the slope of the two curves is equal from day 97 onwards. This appears to be factually inaccurate.