NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Dabrafenib for treating unresectable, advanced or metastatic BRAF^{V600} mutation-positive melanoma [ID605]

Dear [redacted]

The Evidence Review Group, Liverpool Reviews and Implementation Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 30th April 2014 by GlaxoSmithKline UK. 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 **5pm on 4 June 2014.** 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.

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

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Individual trials

A1. **Priority question:** Please provide the protocols and statistical analysis plans for the BREAK-3, COMBI-D and BRF113220 trials.

A2. Table 23 (page 85) of the manufacturer's submission appears to have data for dabrafenib monotherapy from BRF113220 (Part C) entered in the column for dacarbazine from BREAK-3 (and vice versa). Please confirm whether data was entered incorrectly in the table.

A3. It is noted that the progression-free survival (PFS) data for BREAK-3 are from the pre-specified, initial data analysis of 19 December 2011. Please provide the PFS data expressed as a hazard ratio (with confidence intervals) and in absolute terms as medians in months (with confidence intervals) from the most recent data-cut available.

A4. It is noted that even at the most recent data-cut in the manufacturer's submission, the overall survival data from BREAK-3 are immature. If subsequent overall survival data have become available, please provide these and re-calculate the RPSFT adjustment accordingly.

A5. Please provide the absolute values in months (with confidence intervals) for overall survival estimated using the RPSFT model.

A6. It is stated on page120 of the manufacturer's submission that: "*The adjusted median overall survival for dabrafenib within the Phase II BRF113220 study was 448 days or 14.7 months (see Table 92). This provides a more robust estimate of the overall survival benefit of dabrafenib".*

a) Please clarify if Table 92 is the correct table cross-referenced by this text.

b) Please also clarify why this estimate is considered to be more robust than the estimate from BREAK-3.

A7. For BREAK 3 and BRIM-3 please provide updated numbers (and percentages) of patients who:

a) crossed over from the control arm to the treatment arm

b) crossed over from the treatment arm to the control treatment

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

c) received additional treatment on progression in the control arm

d) received additional treatment on progression in the treatment arm.

For (c) and (d), please also provide a breakdown (numbers and percentages) of the treatment received by treatment arm.

Indirect treatment comparisons

A8. **Priority question:** Please provide indirect treatment comparisons using the unadjusted hazard ratios and standard errors, using the most up-to-date data available for BREAK-3 and BRIM-3 (such as data from the recently published paper by McArthur et al 2014). Please also provide the estimates for the adjusted hazard ratios and standard errors using the most up-to-date data if the most up-to-date data were not used in the manufacturer's submission.

A9. It is stated in Table 35 (page101) of the manufacturer's submission that the median follow-up for BRIM-3 was 14 months. Please clarify the source of these data (including page numbers).

Section B: Clarification on cost-effectiveness data

B1**. Priority question: BREAK-3 trial results:** Please provide the following time-to-event Kaplan-Meier analyses using a different censoring rule, that is, patients still alive and at risk should be censored at the time of data cut-off, and *not* the date the patient was last seen or contacted. Re-analysis using a different censoring rule removes a known form of bias (informative censoring) arising when patients still at risk at the time of data cut-off are accorded a reduced exposure time (for example, when last seen, rather than when the trial is terminated). This has the effect of causing the estimated survival curve to dip sharply downward prior to the end of the survival plot, leading to serious misfitting of parametric projective models.

The analyses required are:

a) Kaplan-Meier analysis of post-progression survival (PPS) for each trial arm, and also for the crossover and non-crossover subgroups of the control arm separately. The base case analysis indicates a substantial amount of survival gain arising after a patient's disease has progressed. Providing this data will allow the ERG to assess the extent to which the model output is consistent with the trial evidence.

b) Kaplan-Meier analysis of PFS for each trial arm using the most recent data cut (as per A3 above);

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

c) Kaplan-Meier analysis of OS for each trial arm using the most recent data cut (as per A4 above), and also for crossover and non-crossover subgroups separately;

d) Kaplan-Meier analysis of post-crossover progression-free survival (PFS2) and post-crossover overall survival (OS2) for crossover patients in the control arm.

B2. BREAK-3 baseline data**:** For both the dabrafenib and dacarbazine arms in BREAK-3, please provide a table showing the number of patients in 5-yearly age bands (for example, <44, 45-49, 50-54, etc) by sex (male, female).

Section C: Textual clarifications and additional points

C1. Priority Question: The ERG received a disc of references from the manufacturer for this appraisal. This included the Clinical Study Report for BREAK-3 and a report prepared by Nicholas Latimer and Keith Abrams entitled 'Adjusting for treatment crossover in the BREAK-3 and METRIC clinical trials – Stage 1 feasibility analysis results, February 2013 update'. Please provide guidance on the confidentiality status of the information included in these reports and whether the ERG can quote from these documents without marking them as confidential.

C2. Please confirm whether all the references previously received on the compact disc can be quoted in the ERG report.