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.	Provided as separate attachments.
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.	Thank you for drawing our attention to this. We have provided a version of our submission where this has been corrected.
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-cutavailable.	Our submission discusses PFS results from both the December 2011 data cut and a subsequent June 2012 data cut (see page 87 of our submission document). The indirect comparison and economic model utilise PFS data from the June 2012 data cut. The June 2012 data cut was used for the final analysis of PFS for BREAK-3.
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.	A more recent data cut of OS has become available since we made our submission. Unadjusted ITT Kaplan Meier data from a January 2014 data cut of BREAK-3 is provided below. This has not been adjusted for cross over. A cross over analysis is planned for the final OS analysis of BREAK-3 (expected Q4 2014). GSK are committed to providing NICE with this data once it is available. [redacted]

	[redacted]
A5. Please provide the absolute values in months (with confidence intervals) for overall survival estimated using the RPSFT model.	The medians were not reached because of the re-censoring involved in the RPSFT analysis. This re-censoring was necessary to avoid informative censoring in the counterfactual survival times.
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.	a) There should not be a reference to Table 92. The BRF113220 study is discussed in more detail in Appendix 10.13 of our submission. b) We were not contrasting the unadjusted OS estimate for BRF113220 with the estimate from BREAK-3. Our statement was intended to indicate that the adjusted overall survival estimate from the BRF113220 study is more representative than the unadjusted overall survival estimate from BRF113220 due to the latter being heavily confounded by cross over.
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	These are provided for BREAK-3 (Dec 2012 data cut). 34% of patients crossed over from the control arm to the treatment arm in BRIM-3 (Feb 2012 data cut). We do not have access to patient level data for BRIM-3. **Table 1. Details of crossover and additional treatment** [redacted] BREAK-3, ITT (Dec 2012)

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

Crossed over from the control arm to the treatment arm (n, %)	36 (57%)
Crossed over from the treatment arm to the control treatment (n, %)	0
Received additional treatment on progression in the control arm (n, %) [NB: not including crossover]	13 (21%)
Received additional treatment on progression in the treatment arm (n, %)	80 (43%)

Table 2. BREAK-3: treatments received post-progression (Dec 2012)

Ingredient	GSK2118436 (N=187)	DTIC (N=63)
Any medication	80 (43%)	13 (21%)
IPILIMUMAB	38 (20%)	2 (3%)
DACARBAZINE	21 (11%)	2 (3%)
VEMURAFENIB	10 (5%)	9 (14%)
FOTEMUSTINE	12 (6%)	1 (2%)
CARBOPLATIN	7 (4%)	0
PACLITAXEL	7 (4%)	0
LENVATINIB MESILATE	6 (3%)	0
TEMOZOLOMIDE	5 (3%)	1 (2%)
Medication Not Coded	3 (2%)	1 (2%)
CISPLATIN	3 (2%)	0
INTERLEUKIN-2	2 (1%)	0
INVESTIGATIONAL HUMAN MONOCLONAL ANTIBODY	2 (1%)	0
MITOGEN-ACTIVATED PROTEIN/EXTRACELLULAR SIGNAL-REGULATED KINASE (NOS)	2 (1%)	0
MK-3475	2 (1%)	0
ANASTROZOLE	1 (<1%)	0

	BLEOMYCIN	1 (<1%)	0
	CYCLOPHOSPHAMIDE	1 (<1%)	0
	INVESTIGATIONAL VACCINES	1 (<1%)	0
	LOMUSTINE	1 (<1%)	0
	MEDICATION UNKNOWN	1 (<1%)	0
	VINBLASTINE SULFATE	1 (<1%)	0
	VINDESINE	1 (<1%)	0
	VINDESINE SULFATE	1 (<1%)	0

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.

The PFS endpoint is not confounded by cross over. The indirect treatment comparison (ITC) for PFS presented in our submission utilises the latest data available for BREAK-3 and BRIM-3.

ITC of OS using unadjusted HRs

We have provided results for an ITC of overall survival using unadjusted HRs from the latest data cut from BRIM-3 (Feb 2012) and from the Dec 2012 data cut from BREAK-3 (tables 3 and 4). This has not been updated with the results of the Jan 2014 BREAK-3 data cut. Inclusion of the updated data would not make a substantial difference to the interpretation of the ITC (i.e. that there is no significant difference in overall survival between dabrafenib and vemurafenib). It is also more appropriate to use the December 2012 data cut of BREAK-3 in the ITC as this is more comparable with the BRIM-3 data in terms of median follow-up (see table 5 below). Furthermore we would like to highlight the considerable bias associated with this analysis, as both the BREAK-3 and BRIM-3 trials are confounded by a high proportion of patients switching to active treatment upon progression.

Table 3. OS inputs for indirect treatment comparison of unadjusted OS data

					95% CI	
	Datacut	**Treatment**	**Control**	**HR**	**Lower**	**Upper**
BREAK-3	Dec 2012	Dabrafenib	Dacarbazine	0.76	0.49	1.18
BRIM-3	Feb 2012	Vemurafenib	Dacarbazine	0.76	0.63	0.93

Table 4. Indirect treatment comparison of unadjusted OS data

	Dabrafenib (BREAK-3; Dec 2012) vs.		
	HR	**95% CI**	
Vemurafenib (BRIM-3; Feb 2012)	1.00	0.62	1.62

ITC of OS using adjusted HRs

<table>
<tr>
<td></td>
<td>The ITC for PFS presented within our submission utilises the latest adjusted data available for BREAK-3 (Jun 2102) and BRIM-3 (Feb 2012).

The ITC for OS presented within our submission utilises the latest available adjusted data for BRIM-3 (Feb 2012) and adjusted results from the Dec 2012 data cut for BREAK-3. We do not currently have cross-over adjusted OS results for the January 2014 data cut so are unable to update the ITC with this data. As stated above it is more appropriate to use the Dec 2012 BREAK-3 data as this is more comparable with the data from BRIM-3 in terms of the duration of follow up. As for the ITC using unadjusted HRs, it is also unlikely that inclusion of this latest data cut for BREAK-3 would alter the interpretation of the ITC (i.e. that there is no significant difference in overall survival between dabrafenib and vemurafenib). A sensitivity analysis where a class effect for OS and PFS is assumed has been provided in our submission.

Table 5: Comparison of data cuts
<table>
<tr><th></th><th>BREAK-3 Dec 2012</th><th>BREAK-3 Jan 2014</th><th>BRIM-3 Feb 2012</th></tr>
<tr><td>% Cross over</td><td>57%</td><td>58.7%</td><td>34%</td></tr>
<tr><td>Median follow up (control arm)</td><td>12.7 months</td><td>12.81 months</td><td>9.5 months</td></tr>
<tr><td>Median follow up (treatment arm)</td><td>15.2 months</td><td>18.56 months</td><td>12.5 months</td></tr>
</table>
Note: McArthur et al 2014 report the results of the Feb 2012 data cut of BRIM-3</td>
</tr>
<tr>
<td>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).</td>
<td>This is incorrect. Median follow up for the Feb 2012 data cut of BRIM-3 was 12.5 months for the vemurafenib arm and 9.5 months for the dacarbazine arm. We have provided a copy of our submission where this has been corrected.</td>
</tr>
</table>

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	We understand that the conventional approach to censoring is to censor at last observation or event. We are unaware of any examples where this alternative approach (censor at data cut off) has been used for the purpose of informing economic evaluations conducted as part of a NICE

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 datacut (as per A3 above); 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;	appraisal. We believe that the approach suggested may introduce bias in some instances. Whether this is the case depends on the likelihood of events being observed during the period between the last observation and data cut off. For example, for PFS, events are not observable during the period between the last observation and data cut off. Censoring at data cut off would therefore likely overestimate progression free survival as it would be assumed that all subjects are at risk of progression, when in fact this is not known. For PFS censoring at last observation is associated with less bias. If events are observable during the period between the last observation and data cut off (as may be the case for OS) the standard approach to censoring could result in bias as this would reduce survival times for those who are known to be still at risk and could thus underestimate survival. However, as discussed by Bagust and Beale (2013) the impact of the conventional approach to censoring is that there may be sudden downward movements of the Kaplan Meier plot at the end of the observed data (as a result of there being fewer patients at risk). These sudden downward movements are not observed for the BREAK-3 OS Kaplan Meier data that informs the economic model and is therefore not considered to be an issue for this particular data set. For the reasons outlined above all requested analyses have been performed using the conventional approach to censoring (i.e patients censored at last observation or event). [redacted]

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

[redacted]

[redacted]

a) A Kaplan Meier analysis for PFS2 is provided below (Jun 2012 data cut). OS2 is a repeat of the analysis requested in B1C and is provided above.

Summary of Investigator-Assessed Kaplan-Meier Estimates of Progression-Free Survival in the Crossover Phase

	Crossover GSK2118436 (N=35)
Number of Subjects	
n	35
Progressed or Died (event)	24 (69%)

	Censored, Follow-up ended 2 (6%) Censored, Follow-up ongoing 9 (26%) Estimates for progression-free survival (Months) [1] 1st Quartile 3.3 95% Confidence Interval (2.7,4.2) Median 4.4 95% Confidence Interval (4.1,6.3) 3rd Quartile 6.4 95% Confidence Interval (5.6,8.2)
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).	The requested data is provided below. Summary of Randomized Subjects by Sex and Age Groups SEX: F Dabrafenib (BREAK-3) (N=187) DTIC (BREAK-3) (N=63) Total (N=250) --- Age n 75 26 101 18- <=24 1 (<1%) 2 (3%) 3 (1%) 25- <=29 1 (<1%) 2 (3%) 3 (1%) 30- <=34 1 (<1%) 2 (3%) 3 (1%) 35- <=39 11 (6%) 3 (5%) 14 (6%) 40- <=44 12 (6%) 2 (3%) 14 (6%) 45- <=49 17 (9%) 1 (2%) 18 (7%) 50- <=54 12 (6%) 3 (5%) 15 (6%) 55- <=59 3 (2%) 1 (2%) 4 (2%) 60- <=64 6 (3%) 5 (8%) 11 (4%) 65- <=69 1 (<1%) 2 (3%) 3 (1%) 70- <=74 6 (3%) 1 (2%) 7 (3%) 75- <=79 3 (2%) 2 (3%) 5

(2%)			
80- <=84	1 (<1%)	0	1 (<1%)
90- < 94	0	0	0

Summary of Randomized Subjects by Sex and Age Groups

SEX: M

	Dabrafenib (BREAK-3) (N=187)	DTIC (BREAK-3) (N=63)	Total (N=250)
Age			
n	112	37	149
18- <=24	0	0	0
25- <=29	4 (2%)	1 (2%)	5 (2%)
30- <=34	6 (3%)	0	6 (2%)
35- <=39	8 (4%)	3 (5%)	11 (4%)
40- <=44	9 (5%)	3 (5%)	12 (5%)
45- <=49	8 (4%)	8 (13%)	16 (6%)
50- <=54	14 (7%)	7 (11%)	21 (8%)
55- <=59	16 (9%)	5 (8%)	21 (8%)
60- <=64	17 (9%)	3 (5%)	20 (8%)
65- <=69	13 (7%)	3 (5%)	16 (6%)
70- <=74	8 (4%)	2 (3%)	10 (4%)
75- <=79	5 (3%)	1 (2%)	6 (2%)
80- <=84	3 (2%)	1 (2%)	4 (2%)
90- < 94	1 (<1%)	0	1 (<1%)

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.	The crossover report is pending publication and should be treated as academic in confidence. The ERG can quote from the BREAK-3 clinical study report which is not confidential. However, we would appreciate it if the ERG could let us know what information they wish to use so that we can arrange for this to be available as data on file in case of request.
C2. Please confirm whether all the references previously received on the compact disc can be quoted in the ERG report.	The ERG can quote the references provided.