National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Dabrafenib for treating unresectable, advanced or metastatic BRAFV600 mutation-positive melanoma [ID605]

You are asked to check the ERG report from Liverpool Reviews and Implementation Group (LRiG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **14th July 2014** using the below proforma comments table. Please ensure that you submit this pro-forma to NICE using NICE Docs. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Assessment of the cost-effectiveness of dabrafenib versus vemurafenib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that they are unable to assess the clinical and cost-effectiveness of dabrafenib versus vemurafenib.	We propose that the results of GSK's sensitivity analysis, where a class effect for dabrafenib and vemurafenib is assumed, are presented within the ERG's report.	Our submission provides a sensitivity analysis that incorporates a class effect assumption for dabrafenib and vemurafenib (page	This is not a factual error. The ERG report Table 31 presents the deterministic univariate sensitivity analysis

	This is relevant to the following section: **ERG report. Page 90. Section 8.** "As noted above the ERG demonstrated a lack of validity of the methods used in the ITC and therefore was not able to assess the cost effectiveness of dabrafenib vs vemurafenib."	192 of manufacturer submission). Given that on page 41, the ERG suggest that dabrafenib and vemurafenib are likely to be similar in terms of efficacy, this analysis should be discussed. This analysis is supported by the ITC using unadjusted OS (which yielded a HR of 1.00, 95% CI: 0.62-1.62) as well as the results of the ITCs of PFS and RPSFTM adjusted OS. These ITC results are also supported by the Schilling study which, although unrandomised, found that PFS and OS between dabrafenib and vemurafenib were very similar (Schilling et al, 2014). Thus it is not unreasonable to use a class effect assumption when considering the clinical and cost-effectiveness of dabrafenib and vemurafenib.	for dabrafenib versus vermurafenib. The data related to class effect is based on the ITC which the ERG has demonstrated to be flawed so including results based on that would not be appropriate. Even if the ERG were to state that the results may be similar there is insufficient data to demonstrate this. The cited paper by Schilling et al reports data from a non-randomised study that had unequal patient groups that included both previously treated and treatment naïve patients. It is noted by the authors that overall median PFS and OS in this report are much lower than those reported in the trial data used in the MS. Members of the committee have access to the MS if they want to explore these data.

Issue 2 Significance of RPSFTM adjusted OS data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report does not explain	Current wording:	If the results of an ITT analysis are	Page 7 – Sentence added

why the adjusted OS HR from BREAK-3 is not significant.	**ERG report. Page7, Section 1.3.** "It was not possible to report the median RPSFTM adjusted OS in months but the manufacturer noted that there was no statistically significant difference between treatment arms (Hazard ratio [HR] 0.55,95% Confidence Interval [CI]:0.21 to 1.43)" Proposed addition to this sentence: "This is to be expected as the RPSFTM maintains the p-value of the ITT analysis."	not significant, an adjustment for cross over using RPSFTM can never yield a significant result as the methodology maintains the significance level of the ITT analysis.	This is to be expected as the RPSFTM maintains the p-value of the ITT analysis.

Issue 3 HRQoL results for dabrafenib vs. dacarbazine in BREAK-3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report refers to a poster presentation of HRQoL data (Grob *et a*l 2012) which have been updated and published in full since the time of our submission (Grob *et al* 2014). The updated HRQoL data show statistically significant improvements for dabrafenib over dacarbazine in some domains.	The ERG may wish to amend their report to reflect the HRQoL findings as reported in the Grob publication (Grob *et al*., 2014). This is relevant to the following sections: **ERG report. Page 8. Section 1.3.** " No significant differences between dabrafenib and dacarbazine were reported in BREAK-3 in relation to HRQoL" **ERG report. Page 49. Section 4.6.1.** "A poster presentation by Grob et al 2012 reports no statistically significant differences between patients treated with dabrafenib and dacarbazine for HRQoL. It is however stated that differences in functionality and symptoms at disease progression between the arms were	Grob *et al*., (Ann Oncol 2014) has reported updated HRQoL data from the BREAK-3 study, which was not available during the writing of our submission. Statistical differences in HRQoL between the dabrafenib and dacarbazine arms (as measured by the validated EORTC QLQ-C30 questionnaire) were assessed using mixed-model repeated measure analysis. Although exploratory, the results showed statistically significant improvements from baseline in favour of dabrafenib for 'emotional functioning' at weeks 6 and 12. Statistical differences between arms in favour of	This is not a factual error. The ERG has commented on the evidence provided as part of the submission. The ERG cannot alter its report based on new evidence submitted following submission of the MS. The ERG does note that six of the authors of the Grob et al 2014 paper (published in the same month as the MS) are employees of the manufacturer.

	clinically meaningful in favour of dabrafenib."	dabrafenib were also observed for the symptom dimensions: nausea and vomiting, diarrhoea, fatigue, dyspnoea, appetite loss and insomnia at weeks 6 and/or 12. Additionally, a small but clinically meaningful improvement in 'social functioning' at week 12 was observed in favour of dabrafenib (Grob *et al.*, 2014).	

Issue 4 Inclusion of patients with BRAF^{V600K} mutations

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report states that BRIM-3 eligibility criteria ...allowed entry to patients with BRAF^{V600K} mutations. This is incorrect.	Current wording: **ERG report. Page 9. Section 1.4.** "Both trials included in the ITC (BREAK-3 and BRIM-3) appear to be broadly similar in terms of patient eligibility criteria, the main exception being that BRIM-3 allowed entry to patients with BRAF^{V600K} mutations (8%)." Proposed wording: ""Both trials included in the ITC (BREAK-3 and BRIM-3) appear to be broadly similar in terms of patient eligibility criteria. Patients with V600K were inadvertently enrolled into BRIM-3."	BRIM-3 was not set up to specifically recruit patients with a V600K mutation but inadvertently included them. Inclusion criterion 4 of the BRIM-3 protocol specified: "Patients must have a positive BRAF V600E mutation result determined by a designated laboratory using a Roche CoDx BRAF mutation test prior to administration of study treatment". (Chapman *et al.* NEJM 2011 (Suppl. appendix) The Cobas 4800 BRAF ^{V600} Mutation Test was specifically designed to detect the BRAF^{V600E} mutation, however it was	Page 9 Change made Both trials included in the ITC (BREAK-3 and BRIM-3) appear to be broadly similar in terms of patient eligibility criteria. Patients with V600K were inadvertently enrolled into BRIM-3.

		subsequently found to also detect 70% of BRAF^{V600K} mutations. The inability of the test to distinguish between E and K mutations at that time led to at least 57 trial participants with tumours harbouring the BRAF^{V600K} mutation being enrolled into BRIM-3. (McArthur *et al*. 2014)	

Issue 5 Difference in baseline LDH levels >ULN between BREAK-3 and BRIM-3 trials and potential impact on prognosis of the respective trial populations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG has focused on the proportions of patients within the BRIM-3 and BREAK-3 studies with baseline LDH >ULN as an important factor influencing prognosis, but have failed to consider the respective proportion of patients with M1c stage disease who have the poorest prognosis. The classification of M1c disease includes all patients with baseline LDH>ULN. This is important when considering the credibility of the results of the ITCs.	We propose that the ERG acknowledges that, although there were differences in baseline LDH levels >ULN between the populations in BREAK-3 and BRIM-3, M1c stage is the key determinant of disease prognosis, and that the proportion of patients with M1c stage disease was very similar across the two trials. **This is discussed in Section 1.4. (page 9); Section 1.9.3 (page 13); Section 4.3.3 (page 38); Section 4.8 (page 50) of the ERG report.**	Elevated LDH is a secondary determinant of metastatic staging in Stage IV melanoma; specifically elevated LDH >ULN is included in the M1c sub-category of the AJCC melanoma staging system (Balch 2009). The proportion of patients with stage M1c disease was very similar between the two studies at baseline (BREAK-3, 66%; BRIM-3, 65%). The overall prognosis of any patient with M1c disease is poor regardless of LDH level (1-year OS for patients with metastases to organs other than skin, subcutaneous tissues, lymph nodes or lung 33% [n=4,603] vs. 32% [n=377] for patients with elevated LDH).	This is not a factual error. The ERG acknowledges that disease stage is an important issue. The report however was simply pointing out where there were differences in the groups. .

Issue 6 Whether all relevant evidence has been included

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Although the ERG state that they are reasonably confident that no other relevant published articles exist, they may wish to consider a recent publication by Schilling et al (2014).	The ERG might want to consider the publication by Schilling *et al* when considering whether all relevant evidence has been included. This could be discussed in the following sections: **ERG report. Page 10. Section 1.6.** "The ERG is ... reasonably confident that no other relevant published articles exist." **ERG report. Page 24. Section 4.2.1.** "The ERG is not aware of any additional studies of dabrafenib which are relevant to this appraisal. As no trials directly compared dabrafenib with vemurafenib, the ERG agrees with the manufacturer that it was not appropriate to conduct a meta-analysis."	It has come to our attention that there is, in fact, an additional published article (Schilling *et al.*, 2014) that is relevant to this appraisal. Whilst GSK was not aware of this study at the time of its submission and thus did not include it, we believe that it is relevant to draw your attention to these data. This was an unrandomised study conducted in Germany evaluating 277 vemurafenib-treated patients and 65 who received dabrafenib for BRAF ^{V600} mutation-positive metastatic melanoma. The primary aim was to examine the influence of vemurafenib or dabrafenib on patients' lymphocytes. The median PFS and OS results reported for each arm were very similar and not statistically significantly different between the two treatments (Schilling *et al*., 2014). This is not a GSK sponsored study.	This is not a factual error. See notes above – this is a non-randomised study with a mixed population and therefore would not contribute to this evaluation.

Issue 7 Comment treatment effect assumption in RPSFTM analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report claims that there is no evidence of a treatment benefit for patients who cross over from the dacarbazine arm to receive dabrafenib in BREAK-3.	We propose that the ERG reference the evidence provided within ScHARR's report that investigates the 'common treatment effect' assumption and which provides evidence to support this assumption. This applies to the following sections: **ERG report. Page 11, Section 1.6.** "....the manufacturer has used RPSFTM adjusted data as the basis for modelling OS but there is no evidence that post progression survival in dacarbazine patients crossing over to receive dabrafenib is any different than that of dacarbazine patients who did not cross over." **ERG report. Page 30. Section 4.2.6.** "...the manufacturer's RPSFTM analysis assumes that the effect of receiving dabrafenib is the same when received on diagnosis (i.e. in the dabrafenib group) as it is on disease progression (i.e. in dacarbazine crossover patients). The ERG questions the validity of this assumption as there appears to be no clinical effectiveness evidence to confirm or refute this claim." **ERG report. Page 90. Section 8.** "Importantly, however, this analysis assumes there will be a treatment effect from crossover and does not take into consideration the fact	The ScHARR report (Latimer 2013) on cross over adjustments, provided alongside our submission, provides evidence to support the common treatment effect assumption (pages 41-46). Page 45 of the report states that: "While not conclusive, these analyses suggest that the "common treatment effect" assumption may not be unreasonable for the BREAK-3 trial." In summary, although the analysis conducted by the ERG suggests that there is no difference between those patients in the dacarbazine arm who did and did not cross over, this analysis is associated with considerable selection bias and may be explained by patients who crossed over having a poorer prognosis (see figure 5 of report). ScHARR also conducted an analysis comparing pre-crossover PFS and post-crossover secondary PFS in crossover patients. This demonstrated that PFS after cross over was better than in the initial randomised phase. This is indicative of a treatment effect associated with cross over.	This is not a factual error. The Latimer report states that: 'that currently there is not strong evidence against the "common treatment effect" assumption' However there is also no strong evidence in favour of it either and given all of the uncertainties in immature data no change to the document has been made.

	that there is no evidence of clinical effectiveness related to the use of dabrafenib in patients whose disease has already progressed." **Similar comments in Section 1.9.3 (page 12); Section 4.8 (page 50).**	On the basis of this evidence, the hypothesis of a common treatment effect cannot be rejected.	

Issue 8 Use of follow-up systemic therapy in BREAK-3 trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We believe the data on follow-up systemic therapy in BREAK-3 provided in response to clarification question A7 may have been interpreted incorrectly.	We propose that the text is amended to correctly reflect follow-up systemic therapy received by patients in both treatment arms, including crossover to dabrafenib for the dacarbazine control arm and dabrafenib beyond progression in the dabrafenib experimental arm. This applies to: **ERG report. Page 30. Section 4.2.6** "From trial data made available by the manufacturer at clarification, the ERG notes that 43% of patients in the dabrafenib arm received subsequent treatment whilst 21% of patients in the dacarbazine arm received subsequent treatment. A range of 21 different treatments were administered to patients in the dabrafenib patients including ipilimumab (20%), dacarbazine (11%) and vemurafenib (5%) and seven different treatments were	Table 2 that was provided in response to clarification question A7 could have been more clearly explained in our response. Table 2 excluded any subsequent treatments with dabrafenib. It therefore excluded any mention of crossover to dabrafenib for the control arm and excluded dabrafenib given beyond progression to the experimental arm. In order to provide more clarity the manufacturer has provided Table 6.4010. For clarification, as of the Dec 2012 data cut, the 19% (not 21%) of patients in the dacarbazine arm who received a first subsequent treatment excludes the 36 patients who crossed over to dabrafenib (and the additional patient who received dabrafenib but was not a crossover patient). In total,	No change made The ERG can only consider data submitted as part of the MS and clarification process not data submitted as part of the factual accuracy check and cannot include new data submitted by the manufacturer.

	administered to dacarbazine patients including ipilimumab (3%) and vemurafenib (15%). The ERG does not consider that all patients in the BREAK-3 study received similar treatments at the time of disease progression or that patients in both groups received treatments that are routinely available in UK clinical practice." **ERG report. Page 90. Section 8.** "The MS also failed to consider whether the subsequent treatments received by patients in both arms were sufficiently similar and/or reflected current practice, important requirements underlying the RPFSTM since subsequent treatments other than the treatment of interest can also influence OS."	78% (49/63) of patients randomised to dacarbazine received follow-up systemic therapy. This compares with 55% (not 43%) of patients who received follow-up systemic therapy in the dabrafenib arm. The follow-up systemic therapies received by the majority of patients in treatment arms were those that would be expected in clinical practice in this patient population i.e. targeted agents (dabrafenib or vemurafenib), immunotherapies (ipilumumab, interleukin) and chemotherapy agents (dacarbazine, temzolomide, fotemustine, carboplatin/paclitaxel). Of the 21 different therapies received by dabrafenib patients, 15 therapies were received by only one patient each.	

Issue 9 Number of patients who crossed over from dacarbazine arm to dabrafenib therapy in BREAK-3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
We believe there is a typographical error in this sentence: **ERG report. Page 26. Section 4.2.6.** "At the time of the analysis, it is	Original wording: "At the time of the analysis, it is reported in the MS that 37 (57%) crossed over from dacarbazine to dabrafenib." Proposed amendment:	The figure 37 is incorrect (if it is specifically referring to 'crossover' patients in BREAK-3). At the time of the December 2012 data cut for OS, 36 patients (57%) had crossed over from the	Pg 29 Change made Note that the number 37 has not been changed on page 72 as the updated figure is what was used as part of the economic modelling.

reported in the MS that 37 (57%) crossed over from dacarbazine to dabrafenib.”	At the time of the analysis, it is reported in the MS that **36** (57%) crossed over from dacarbazine to dabrafenib	dacarbazine arm to dabrafenib treatment*. By the December 2012 data cut, one additional patient from the dacarbazine arm had received dabrafenib but who did not cross over within the study and was therefore not considered to be a ‘crossover’ patient*. [One additional patient had crossed over from the dacarbazine arm to dabrafenib by the time of the January 2014 data cut (=37/63, 59% crossover)]. * Note: Patients who crossed over had to have independently verified disease progression using RECIST 1.1 criteria; those who did not crossover did not have to have disease progression (e.g., they could stop dacarbazine because of an AE).	

Issue 10 **OS medians/HRs for dacarbazine arm in BRIM-3 differ between Manufacturer’s Submission and those used by ERG**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG does not seem clear as to where GSK has obtained their OS data for the dacarbazine arm in BRIM-3 (HR and median OS).	We suggest that a clearer explanation is provided as to why there are differences in the data presented within our submission and those used by the ERG.	The manufacturer’s submission uses uncensored data as reported in the NICE Guidance for vemurafenib (TA 269 Dec 2012) i.e. median OS for dacarbazine 10.3	Page 36 Change made The BRIM-3 OS HR used in the manufacturer’s ITC is the uncensored result taken directly from the vemurafenib

	Original wording: **ERG report. Page 36. Section 4.3.2.** "The BRIM-3 OS HRs used in the manufacturer's ITC differ slightly from those published by McArthur et al. This could be due to differences in the analysis techniques that were used to generate them." Proposed wording: "The BRIM-3 OS HR used in the manufacturer's ITC is the uncensored result taken directly from the vemurafenib NICE Guidance (TA 269). "	months (uncensored HR 0.76; 95% CI: 0.63-0.93). The ERG has used data censored at crossover as reported in the recent publication by McArthur *et al*. i.e. median OS for dacarbazine 9.7 months (censored HR 0.70; 95% CI: 0.57-0.87).	NICE Guidance (TA 269).

Issue 11 Number of treatment-related fatal AEs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The number of treatment related fatal AEs in BREAK-3 requires updating.	Original wording: **ERG report. Page 43. Section 4.5.** "Fatal AEs were rare and no fatal AEs relating to study treatment were reported in any study ." Proposed amendment: Fatal AEs were rare and only one fatal AE possibly related to study treatment were reported.:	As of the December 2011 safety data presented in the BREAK-3 CSR, no treatment-related fatal AE had been reported in either the dabrafenib or dacarbazine arm in BREAK-3. Although inadvertently not reported in our submission, we wish to inform you that according to updated safety data from the June 2012 data cut, one patient in the dabrafenib arm had died due to fatal SAEs (myocardial infarction/acute coronary syndrome) considered possibly related to study treatment (Hauschild *et al*., 2013).	Page 43 Change made Fatal AEs were rare and only one fatal AE possibly related to study treatment was reported.

Issue 12 PPS gain sensitivity analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
It is not clear what the ICERs presented in the section below are comparing. **Page 68. Section 5.5.1.** "The importance of the large estimated values for PPS gain ascribed to dabrafenib becomes clear from the sensitivity of the manufacturer's ICER to alternative assumptions: if only 50% of the PPS gain in the manufacturer's base case is considered realistic, the ICER increases by about 45% to over £70,000 per QALY gained; if there is no additional survival advantage from dabrafenib beyond disease progression, the ICER more than doubles to over £120,000 per QALY gained."	We propose that it is made clear that the ICERs presented are for dabrafenib versus dacarbazine and that the respective ICERs for dabrafenib versus vemurafenib are provided.	It is not clear what these ICERs are comparing. Only ICERs versus dacarbazine are presented. These may be perceived to be ICERs for dabrafenib versus vemurafenib.	This is not a factual error. Since only ICERS comparing dacarbazine are given it is clear what is being reported. The section where this is written is related to the base case model. Adding ICERs for vemurafenib would add confusion.

Issue 13 Assessment of parametric curve fit to trial data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In addition to AIC/BIC statistics, an AUC (area under the curve) analysis and visual inspection were used in order to select	We propose that the wording is amended to clarify that we also used an AUC analysis and visual inspection.	As stated in the manufacturer's submission, AUC analysis and visual inspection were also used to choose the most appropriate	Pages 69 Changed to: "The use of a log-normal

appropriate parametric functions. This section of critique refers to the trial segment of modelling and does not use the tail of the distribution.	This applies to the following section: ERG report. Page 69. Section 5.5.1. “The use of a log-normal distribution to represent the trial survival data is based on comparison of Akaike and Bayesian information criteria scores (AIC/BIC). However, such a comparison is not definitive as the basis for choosing a parametric function as the significance of small score differences is difficult to interpret, and also assumes that the ‘true’ distribution is included in the set of five candidate distributions being compared (exponential, Weibull, log-normal, log-logistic and gamma). In particular, the log-normal distribution is known to exhibit a ‘long tail’ which tends to exaggerate long-term survival.”	parametric function. This section of critique refers to the trial segment of OS modelling which does not make use of the tail of the curve. However, a long tailed distribution such as the log normal distribution may be appropriate in cases where there are a proportion of patients experiencing long term benefits.	distribution to represent the trial survival data is based on comparison of Akaike and Bayesian information criteria scores (AIC/BIC) and correspondence of AUC estimates (Tables 130 & 131 of MS). However, such a comparison is not definitive as the basis for choosing a parametric function. The significance of small AIC/BIC score differences is difficult to interpret, and also assumes that the ‘true’ distribution is included in the set of five candidate distributions being compared (exponential, Weibull, log-normal, log-logistic and gamma). For neither AUC nor AIC/BIC is a single functional form clearly superior across all comparisons in the manufacturer’s analyses, and the log-normal distribution is known to exhibit a ‘long tail’ which tends to exaggerate long-term survival. A more fundamental problem is that using the full data set as the basis for projecting the experience of the minority of patients still alive (at risk) at the end of trial fails to recognise the strong influence of survivor bias altering the case-mix and risk

			profile of long-term survivors compared to the original randomized population. This can only be overcome by concentrating curve-fitting on the data (events) towards the end of the trial. ”

Issue 14 Calculation of dacarbazine cost

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that the manufacturer failed to recognise that gender is an important factor in calculating the average dose and related cost of a medicine.	We propose the ERG acknowledge that the manufacturer’s approach took into account weight and BSA distributions from BREAK-3. ERG report. Page 84. Section 6.1.3. “In estimating the acquisition cost of dacarbazine the manufacturer has assumed that BSA conforms to a log-normal distribution with a mean of 1.926 and standard deviation of 0.224. This is incorrect as BSA within the general population conforms to a normal distribution and, unlike body weight which is best represented by the log-normal function. In addition, the manufacturer has failed to recognise that gender is an important factor when calculating the average dose and related cost of medication.”	Weight and BSA distributions were taken from BREAK-3 so reflect the age and sex distribution in the trial. A log-normal distribution provided a good fit to the BSA data.	Page 84 Changed to: “In estimating the acquisition cost of dacarbazine the manufacturer has assumed that BSA conforms to a log-normal distribution with a mean of 1.926 and standard deviation of 0.224. This is incorrect as BSA within the general population and in cancer chemotherapy populations (ref Sacco [54]) conforms to a normal distribution, unlike body weight which is best represented by the log-normal function. In addition, the manufacturer has failed to recognise that

			separate analysis by gender is an important factor when calculating the average dose and related cost of medication.”

References:

Chapman PB, Hauschild A, Robert C, *et al*. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. Supplementary Appendix. New England Journal of Medicine 2011;364.

McArthur GA, Chapman PB, Robert C, *et al*. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014 Mar;15(3):323-32.

Balch CM, Gershenwald JE, Soong SJ, *et al*. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009 Dec 20;27(36):6199-206.

Hauschild A, Grob JJ, Demidov LV, *et al*. An update on BREAK-3, a phase III, randomized trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM). Poster and abstract presented at ASCO annual meeting 2013. J Clin Oncol 2013; 31 (suppl): Abstract 9103.

Grob JJ, Amonkar MM, Martin-Algarra S, *et al*. Patient perception of the benefit of a BRAF inhibitor in metastatic melanoma: quality-of-life analyses of the BREAK-3 study comparing dabrafenib with dacarbazine. Ann Oncol 2014 Published online Apr 25.doi: 10.1093/annonc/mdu154

Schilling B, Sondermann W, Zhao F, *et al*. Differential influence of vemurafenib and dabrafenib on patients' lymphocytes despite similar clinical efficacy in melanoma. Ann Oncol 2014 Mar;25(3):747-53.