Dabrafenib for treating unresectable, advanced or metastatic BRAF V600 mutation-positive melanoma: an Evidence Review Group Perspective

Nigel Fleeman, Research Fellow[1*]

Adrian Bagust, Professor[1]

Sophie Beale, Research Associate[1]

Angela Boland, Assistant Director[1]

Rumona Dickson, Director[1]

Kerry Dwan, Research Fellow[1]

Marty Richardson, Research Fellow[1]

Yenal Dundar, Research Fellow[1]

Helen Davis, Acting Director[2]

Lindsay Banks, Medicines Information Pharmacist[2]

[1] Liverpool Reviews and Implementation Group, University of Liverpool, L69 3GB, UK

[2] North West Medicines Information Centre, Liverpool, L69 3GF, UK

Running title: Dabrafenib for metastatic BRAF V600 melanoma

*Corresponding author:

Nigel Fleeman

Whelan Building

University of Liverpool L69 3GB

Tel: 0151 794 5067

Email: nigel.fleeman@liverpool.ac.uk

Word count (abstract): 448

Word count (excluding abstract, headings, table and references): 5836

Key Points for Decision Makers

- The most relevant comparator to dabrafenib in clinical practice today is vemurafenib. No direct evidence comparing these two drugs exists and so an indirect treatment comparison (ITC) was conducted. However, the statistical assumptions required for the conduct this ITC were not considered to be valid by the Evidence Review Group (ERG).
- In the ERG's view, the lack of a robust ITC precluded a credible assessment of the relative cost-effectiveness of dabrafenib to vemurafenib. In addition the assessment of the model used to compare the cost-effectiveness of dabrafenib to dacarbazine identified additional issues which undermined its credibility, most importantly the methods used to project overall survival were not based on trial data.
- The overall costs of treatment with dabrafenib were considered to be similar to the overall costs of treatment with vemurafenib.

Abstract

The National Institute for Health and Care Excellence (NICE) invited GlaxoSmithKline, the manufacturer of dabrafenib, to submit evidence for the clinical and cost effectiveness of dabrafenib for the treatment of unresectable, advanced or metastatic BRAF V600 mutation positive melanoma in accordance with the Institute's Single Technology Appraisal (STA) process. The Liverpool Reviews and Implementation Group (LRiG) at the University of Liverpool was commissioned to act as the Evidence Review Group (ERG). This article summarizes the ERG's review of the evidence submitted by the company and provides a summary of the Appraisal Committee's (AC) final decision in October, 2014.

The clinical evidence for dabrafenib was derived from an ongoing phase III randomized double-blind placebo-controlled international multicentre clinical trial (BREAK-3) involving 230 patients randomized 2:1 to receive either dabrafenib or dacarbazine. A significant improvement in median PFS but not OS was reported in the dabrafenib arm compared to dacarbazine. Vemurafenib is considered a more appropriate comparator than dacarbazine. The clinical evidence for vemurafenib was derived from a completed phase III randomized double-blind placebo-controlled international multicentre clinical trial (BRIM-3) involving 675 patients randomized 1:1 to receive either vemurafenib or dacarbazine. A significant improvement in median PFS and OS was reported in the vemurafenib arm compared to dacarbazine. As there is no direct evidence comparing dabrafenib vs vemurafenib, the company presented an indirect treatment comparison (ITC) that demonstrated no statistical differences between dabrafenib and vemurafenib for PFS or OS. The ERG expressed concerns with the ITC, mainly in relation to the validity of the assumptions underpinning the methodology; the ERG concluded this resulted in findings which are unlikely to be robust or reliable.

Dabrafenib and vemurafenib are both available to patients treated by the NHS in England via a Patient Access Scheme (PAS) in which the costs of the drugs are discounted. Using these discounted costs, the incremental cost effectiveness ratios (ICERs) generated by the company were £60,980 per quality adjusted life year (QALY) for dabrafenib vs dacarbazine and £11,046 per QALY gained for dabrafenib vs vemurafenib. The ERG considered the economic model structure developed by the company to derive the ICERs to be overly complex and based on unsubstantiated assumptions, most importantly in relation to the projection of OS. Applying the latest OS data from BREAK-3 to a less complex model structure increased the estimated ICER for dabrafenib compared with dacarbazine from £60,980 to £112,727 per QALY gained. Since the results from the ITC were considered by the ERG to be neither reliable nor robust, the ERG

also considered a cost-effectiveness comparison to be inappropriate due to a lack of meaningful or reliable data.

In spite of limitations in the data, the AC took the view that dabrafenib and vemurafenib were *'likely'* of similar clinical effectiveness. Since the overall costs of these two drugs were similar, the AC recommended the use of dabrafenib in patients with unresectable, advanced or metastatic BRAF V600 mutation-positive melanoma.

1 Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organization responsible for providing national guidance to the NHS in England on a range of clinical and public health issues, as well as the appraisal of new health technologies. The NICE Single Technology Appraisal (STA) process is specifically designed for the appraisal of a single health technology for a single indication, where most of the relevant evidence lies with one company [1]. Typically, the process is used for new pharmaceutical products close to launch. The evidence for a STA is principally derived from a submission by the company that manufactures the technology and is based on a specification developed by NICE. The company's submission is critiqued by members of the independent Evidence Review Group (ERG) who produce a report to be considered by a NICE Appraisal Committee (AC).

The AC considers the submissions from the company and the ERG alongside testimony from experts, patients and other stakeholders to formulate preliminary guidance or a final determination. This article presents a summary of the ERG report for the STA of dabrafenib for the treatment of unresectable, advanced or metastatic BRAF V600 mutation positive melanoma.

Full details of all relevant appraisal documents (including the appraisal scope, ERG report, company and consultee submissions, NICE guidance and comments on each of these) can be found on the NICE website [2].

2 The Decision Problem

Malignant melanoma is one of the most aggressive forms of skin cancer and is currently the fifth most common cancer in the UK with incidence rates on the rise as evidenced by the fact that from 1999-2001 there were 11 cases/100,000 population while in the period 2008-11 there were 17/100,000 population [3]. In the UK in 2010 there were over 12,000 new cases diagnosed and over 2,000 deaths [3]. Metastatic disease is seen in about 20 % of patients [4] while BRAF V600 mutations are found in around 50 % of melanomas [5]. Although the majority of melanomas (80 to 90 %) are diagnosed as local tumours that can be surgically removed, 2 to 8 % of patients have metastatic disease (Stage III and IV) on initial presentation. [6, 7] Patients with Stage III disease have a 5-year survival rate of 40 to 80 %, [8] while those with Stage IV disease have a much poorer prognosis with median survival times of only 6 to 18 months.

Those with metastasis to the brain have an even poorer prognosis and a life expectancy of only 3 to 5 months. [9]

Until recently, systemic first-line treatment for patients with unresectable, advanced or metastatic BRAF V600 mutation-positive melanoma has been with dacarbazine, a treatment known to be of limited effectiveness [10, 11]. In late 2012 NICE approved the use of vemurafenib to treat unresectable, advanced or metastatic BRAF V600 mutation-positive melanoma [12]. In addition NICE has previously approved ipilimumab for both first and second-line treatment of any patient regardless of BRAF status [13, 14]. Dabrafenib is an alternative BRAF inhibitor to vemurafenib. It has received marketing authorization in Europe as monotherapy 'for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.' [15]

NICE developed a scope for the assessment of dabrafenib within its licensed indication as monotherapy for unresectable or metastatic melanoma in patients with BRAF V600 mutation. [15] The NICE scope indicated that the comparator treatments for patients who were treatment naïve were dacarbazine and vermurafenib and in patients who had been previously treated with dacarbazine (or temozolomide for patients with brain metastasis), ipilimumab or vemurafenib. It is worth noting that during the timeframe of this appraisal process, NICE had approved ipilimumab for treatment naïve patients as well as for patients after initial treatment failure. The specified outcomes to be considered were progression free survival (PFS), overall survival (OS), response rate, adverse effects (AEs) and health related quality of life (QoL). The scope specified that the cost effectiveness of the treatment should be presented in terms of the incremental cost per quality-adjusted life year (QALY) gained using a lifetime horizon that was sufficiently long to reflect differences in costs or outcomes between the technologies. Costs were to be considered from an NHS and Personal Social Services perspective. No specific subgroups of patients and no potential equity or equality issues were identified.

3 Independent Evidence Review Group Report

The evidence provided by the company comprises an initial submission and the company's response to the ERG's request for clarification. The ERG report [16] is a critical review of the evidence for the clinical and cost effectiveness of the technology. It has the following three aims:

- To assess whether the company's submitted evidence conforms to the methodological guidelines issued by NICE

- To assess whether the company's interpretation and analysis of the evidence are appropriate
- To indicate the presence of other sources of evidence or alternative interpretations of the evidence that could help inform the development of NICE guidance

In addition to providing this detailed critique, the ERG modified a number of key assumptions and parameters within the company's economic model to examine the impact of such changes on cost effectiveness results.

The primary evidence in the submission [11] was derived from a randomized control trial called BREAK-3 [17] which compared dabrafenib to dacarbazine. In order to compare dabrafenib to vemurafenib, an indirect treatment comparison (ITC) was required utilising additional evidence from BRIM-3, [18] which compared dacarbazine to vemurafenib. Each of these trials addressed the use of the drugs in treatment naïve patients. No evidence related to the use in previously treated patients was submitted. In addition the ERG used data provided from the company including the BREAK-3 clinical study report [19]. Secondary supporting evidence from other trials assessing the use of dabarafenib was provided, two RCTs (Phase III BRF113220 [20] trial and Phase II Combi-d [21] trial) and two Phase II non-RCTs (BREAK-2 [22] and BREAK-MB [23]). However this evidence involved patient populations and comparators that were different to those specified in the NICE decision problem and thus precluded their inclusion in any quantitative synthesis.

3.1 Clinical Evidence

BREAK-3 [17] was a randomized, open-label, multi-centre (70) phase III trial carried out in 12 countries (but not the UK) between December 2010 and September 2011. Patients were randomized in a 2:1 manner to receive either oral dabrafenib 10 mg twice daily (n=167) or intravenous dacarbazine 1000mg/m^2 every 3 weeks (n=63). The primary outcome was investigator assessed PFS and the initial data cut-off for this outcome was December 2011 with a subsequent data-cut for PFS in June 2012. Secondary outcomes relevant to the decision problem were OS, overall response rate (ORR) (i.e. complete or partial response on RECIST version 1.1), AEs and HRQoL. Follow-up for OS continues with the latest data analysis in December 2012. BREAK-3 [17] allowed patients to cross over to dabrafenib treatment if their disease progressed. At the time of the final PFS data analysis, 57 % of patients had crossed over to receive dabrafenib. In order to consider the potential effect of crossover on OS, the Rank

Preserving Structural Failure Time method (RPSFTM) was employed. The median length of follow-up for PFS (June 2012) was 10.5 months for dabrafenib and 9.9 months for dacarbazine; for OS (December 2012) it was 15.2 and 12.7 months respectively.

BRIM-3 [18] was a randomized, open-label, multi-centre (104) phase III trial carried out in 12 countries (including the UK) from January to December 2010. Patients were randomized in a 1:1 manner to receive either oral vemurafenib 240 mg eight times daily (n=337) or intravenous dacarbazine 1000mg/m^2 every 3 weeks (n=338). Joint primary outcomes were OS and investigator assessed PFS. Secondary outcomes relevant to the decision problem were ORR (i.e. complete or partial response on RECIST version 1.1), AEs and HRQoL. BRIM-3 [18] allowed patients to cross over to vemurafenib treatment if their disease progressed. At the time of the final OS data analysis, 34 % of patients had crossed over to receive vemurafenib. In order to consider the potential effect of crossover on OS, OS censored at the time when patients in the dacarbazine group crossed over to receive vemurafenib was presented in the published paper reporting final OS results [18]. However, in the STA for vemurafenib for locally advanced or metastatic BRAF V600 mutation positive malignant melanoma, [12] OS was also adjusted using the RPSFTM. The median length of follow-up for both OS and PFS was 12.5 months for the vemurafenib arm and 9.5 months for the dacarbazine arm.

Compared to dacarbazine, both trials reported apparent improvements in PFS, OS and ORR (Table 1). The improvements in PFS were statistically significant, differences in median PFS being 4.2 months for dabrafenib and 5.3 months for vemurafenib. A statistically significant improvement in OS of 3.3 months has also been reported for vemurafenib. The reported improvement in OS of 2.6 months for dabrafenib is not statistically significant but the data are still immature as not all planned events (deaths) have occurred. When OS was adjusted using the RPSFTM, a significant improvement was reported for vemurafenib vs dacarbazine but not dabrafenib vs dacarbazine.

In order to compare dabrafenib to vemurafenib, the company carried out ITCs for PFS and OS using the adjusted ITC methodology described by Bucher [24]. Initially, inputs for the ITC for OS were crossover adjusted results (using the RPSFTM) from BRIM-3 [18] (February 2012 data-cut) and BREAK-3 [17] (December 2012 data-cut). The results were described by the company as showing a trend in favour of dabrafenib over vemurafenib for both PFS and OS but the treatment difference was not found to be statistically significant for either outcome. At the request of the ERG, the unadjusted OS hazard ratios were input into the ITC instead of the

RPSFTM adjusted OS hazard ratios. The unadjusted OS results suggest that dabrafenib and vemurafenib may be of equal clinical efficacy. The ITC findings are summarized in Table 2.

Both trials were considered by the company to have low risk of bias. However several differences in the characteristics of the two included trials were identified by the company including differences in sample sizes, ratios of randomization and timings of follow-up. It was unclear if this would impact on any ITC between the two trials.

Dabrafenib was reported to be associated with a manageable safety profile. Notably, pyrexia was more common with dabrafenib than dacarbazine (31 % vs 10 % respectively), although the maximum severity of pyrexia in BREAK-3 [17] was Grade 3 (3 % vs 0 respectively). Although there are no head-to-head data comparing dabrafenib to vemurafenib, pyrexia was less common in the vemurafenib arm in BRIM-3 [25] (16 %, all Grade 1). On the other hand, dabrafenib appears to be associated with a lower incidence of certain types of hyperproliferative skin toxicities than vemurafenib: in BREAK-3 [17], 6 % of patients reported cutaneous SCC/keratoacanthoma (2 % Grade 3 events) compared to 17 % cutaneous SCC (16 % Grade 3) and 9 % keratoacanthomas (all Grade 3). Photosensitivity was also less common in the dabrafenib arm of BREAK-3 [17] compared to the vemurafenib arm of BRIM-3 [25]: 3 % vs 33 % respectively (Grade 3 photosensitivity: 0 vs 3 % respectively).

HRQoL data were only presented for the BREAK-3 trial [17]. Descriptive statistics on EQ-5D utility index in the BREAK-3 study were presented by the company; the mean change in EQ-5D utility index score from baseline to week 15 was lower in the dabrafenib arm (+0.053) than in the dacarbazine arm (+0.128). It was also argued by the company that photosensitivity can have a 'significant effect' on HRQoL which as noted above was lower in patients treated with dabrafenib than those treated with vemurafenib [11].

3.1.1 Critique of Clinical Evidence and Interpretation

Both the BREAK-3 [17] and BRIM-3 [18] are of good methodological quality with minimum risk of bias. The patient populations appear to largely reflect people who would normally be eligible for dabrafenib and vemurafenib outside of the clinical trial setting. However, the ERG did note that the characteristics of the patients in the two included trials may not be wholly comparable. In respect to age, sex, ethnicity, ECOG performance status and tumour, node, metastases staging at screening, the two trials appeared to be very similar but in BRIM-3 [18] a greater proportion of patients had lactate dehydrogenase (LDH) levels above the upper limit of the

normal range than in BREAK-3 [17] (58 % vs 34 % respectively). As the level of LDH has been shown to result in worse PFS and OS, [8, 26] patients in both arms of the BRIM-3 [18] trial might be expected to have worse outcomes than those in the BREAK-3 [17] trial. Indeed, it was noted that median OS did differ in the dacarbazine arms of the trials, being lower in BRIM-3 [18] (9.7 months) than BREAK-3 [17] (15.6 months). This may be indicative of differences in the patient population and/or differences in subsequent treatment received following disease progression in the two trials.

As noted above, 57 % of patients in BREAK-3 [17] crossed over to receive dabrafenib and in BRIM-3 [18], 34 % of patients crossed over to receive vemurafenib. In total, 78 % of patients in the dacarbazine arm of BREAK-3 [17] received additional treatment on disease progression compared to 55 % of patients in the dabrafenib arm. As summarized in Table 3, the most common type of treatment received varied by arm. Detailed information on post-progression treatment for BRIM-3 [18] has not been published but in a response [27] to the first ACD for the vemurafenib STA (vemurafenib for locally advanced or metastatic BRAF V600 mutation positive malignant melanoma [12]), the manufacturer of vemurafenib noted second-line use of ipilimumab in the dacarbazine arm was 19 % compared to 13 % in the vemurafenib arm.

In relation to the BREAK-3 [17] trial, the ERG is not of the opinion that the RPSFTM is an appropriate method of adjustment for crossover for three key reasons. First, survival data from the BREAK-3 [17] study are immature; the results are based on an interim analysis with few deaths. Second, the company'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. Third, treatments received on disease progression in the dacarbazine arm and in the dabrafenib arm should be similar and typical of clinical practice. Aside from differences in types of the first systemic therapy received on disease progression noted above, 32 % of patients in the dacarbazine arm received two or more lines of treatment following disease progression (and a range of 12 treatments in total) whereas in the dabrafenib arm it was 19 % (and a range of 23 treatments in total). Therefore, from trial data made available by the company the ERG did not consider that all patients in the BREAK-3 [17] 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. Furthermore, as part of its critique of the cost-effectiveness evidence (see 3.2.2 below), the ERG found that patients who crossed over to

receive dabrafenib did not gain any significant benefit over the patients who did not crossover meaning the need to adjust for crossover was not in fact warranted.

Regardless of whether there was a need to adjust OS for treatment crossover, the ERG is of the opinion that an ITC using RPSFTM adjusted estimates should constitute a sensitivity analysis rather than the primary analysis. Therefore, as noted above, the ERG requested the company also conduct the ITC with unadjusted OS from both BREAK-3 [17] and BRIM-3 [18] which suggested that dabrafenib and vemurafenib may be of equal clinical efficacy. However, the ERG was not convinced the results from the ITC were robust because three key assumptions did not hold. First, constant proportional hazards were required for both PFS and OS data within the BREAK-3 [17] trial (dabrafenib vs dacarbazine). Analyses conducted by the ERG indicated a significant deviation from constant HR between the trial arms for PFS ($p<0.001$, chi-squared test) but not for OS ($p=0.91$). Second, constant proportional hazards were also required for both PFS and OS data within the BRIM-3 [18] trial (vemurafenib vs dacarbazine). ERG analyses indicated significant deviations from this assumption for both outcomes ($p<0.001$ for PFS, $p<0.001$ for OS, chi-squared test). Finally, PFS and OS data for dacarbazine within the two trials should be broadly comparable and conform to a constant proportional hazard relationship. Comparison of dacarbazine PFS and OS data indicated that PFS hazard profiles were not significantly different ($p=0.46$); however constant proportion hazards were not supported for OS ($p<0.001$).

Regarding safety, the ERG noted that no significant differences between dabrafenib and vemurafenib were reported for any of the types of AEs analysed in a separate report conducted on behalf of the company [28]. Dabrafenib was however reported to be associated with significantly fewer incidences of diarrhoea, nausea, and photosensitivity than vemurafenib. The incidence of all-grade and Grade 3 cutaneous SCC, keratoacanthomas and arthralgia were also reported to be higher with vemurafenib whereas pyrexia, hyperkeratosis and palmar-plantar erythrodysesthesia (PPE) syndrome were more common with dabrafenib.

Data on HRQoL were limited in the company's submission [11].

3.1.2 Evidence Review Group Conclusions on the Submitted Clinical Evidence

Based on current clinical practice, vemurafenib is a more appropriate comparator for dabrafenib then dacarbazine. Unfortunately, the ERG is also of the opinion that there is no robust evidence available to enable a credible comparison of the clinical effectiveness of

dabrafenib vs vemurafenib. This is because three key assumptions regarding constant proportional hazards required for the conduct of the ITC did not hold. While dabrafenib and vemurafenib have some AEs in common, there are notable differences between the two drugs for a number of AEs. Specifically, hyperproliferative skin toxicities (cutaneous SCC and keratoacanthomas), photosensitivity and arthralgia appear to be more common and more severe with vemurafenib whereas pyrexia, hyperkeratosis and PPE syndrome appear to be more common with dabrafenib. There are no comparative quality of life data for dabrafenib and vemurafenib. It is worth noting that photosensitivity, when discussed as part of the STA for vemurafenib, was described as not clinically important. However, during this appraisal clinicians identified it as a major limiting factor in terms of quality of life in the use of vemurafenib.

3.2 Cost effectiveness Evidence

The company undertook a de novo economic evaluation of dabrafenib (intervention) compared with dacarbazine or vemurafenib (comparators) for the first-line treatment of patients with locally advanced or metastatic BRAF V600 mutation positive malignant melanoma. The economic model took an NHS perspective; the time horizon was 30 years; and costs and outcomes were discounted at 3.5 %. The model comprised three states (PFS, post-progression survival [PPS], and death) and used a cycle length of 1 week. All patients started in the PFS state. At the end of each cycle, patients remained in PFS, moved to PPS, or died. Death was an absorbing health state.

Modelled PFS and OS distributions were segmented into two periods, the trial period and the projection period. For both the trial and projection periods, PFS estimates for dabrafenib and dacarbazine were derived from parametric survival distributions fitted to investigator-assessed PFS from BREAK-3 [17] (June 2012 data cut). Constant proportional hazards were used to model PFS for vemurafenib. During the trial period (from randomization until 1.8 years) the OS projection for dabrafenib was based on an independent parametric survival distribution fitted to individual patient data from BREAK-3 [17] (December 2012 data cut), the dabrafenib vs dacarbazine RPSFTM adjusted HR from BREAK-3 [17] was used to project dacarbazine OS and constant proportional hazards were the basis for modelling OS for vemurafenib. For the period from the end of the trial period out to 10-years, survival for patients receiving dabrafanib was based on a parametric survival curve fitted to American Joint Committee on Cancer (AJCC) registry data [8]. Constant proportional hazards (the same values as used in the trial period) were used to model survival for dacarbazine and vemurafenib. Beyond 10 years, survival was based on UK general population mortality data.

Utility values incorporated into the model were those derived from BREAK-3 [17]. In the absence of equivalent data for patients receiving vemurafenib it was assumed that the HRQoL of these patients was the same as that for patients who received dabrafenib. Costs incorporated in the company's model included drug costs (calculated using a confidential discounted cost as agreed as part of the NHS PAS), dispensing costs for dabrafenib and vemurafenib, administration cost for dacarbazine, BRAF V600 mutation testing, anti-cancer therapy after the study, costs associated with health states and AEs and one-off costs for starting treatment and for death. The main sources of cost data used in the model were the NHS Reference Cost Schedule (12-13), the British National Formulary and the results of a cost-of-illness study commissioned by the company (GSK data on file).

The company's base-case incremental cost-effectiveness ratio (ICER) for dabrafenib vs dacarbazine for the first-line treatment of locally advanced or metastatic BRAF V600 mutation positive malignant melanoma was £60,980 per quality adjusted life year (QALY) gained and £44,088 per life year gained. The ICERs for dabrafenib vs vemurafinib were £11,046 per QALY gained and £7,522 per life-year gained. The company's probabilistic analysis showed that at a maximum acceptable ICER of £30,000 per QALY, dabrafenib would have a 6 % probability of being cost effective compared with dacarbazine and a 56 % probability compared with vemurafenib. The company also conducted a series of deterministic sensitivity analyses. For the comparison with dacarbazine, OS was the key driver of the cost-effectiveness results and the key driver for the comparison with vemurafenib was the PFS assumption (alternative survival functions for PFS were explored).

3.2.1 Critique of Cost effectiveness Evidence and Interpretation

The spreadsheet model submitted by the company was considered by the ERG to be more complex than would normally be considered necessary, or appropriate, for the relatively simple logical structure of a three-state transition model. As a consequence, the ERG struggled to trace the logic trails for normally straightforward aspects of such a model. Another difficulty with this structure is that it only allows results for a single regimen to be generated at a time. Incremental comparisons and incremental cost-effectiveness ratios (ICERs) can only be obtained by generating and saving costs and outcomes separately for each regimen, before they can be combined to give the final result.

In the company's model, the ERG noted that the majority of the estimated incremental QALYs arise from estimated life-years in post-progression survival (PPS) (62 % for dabrafenib vs dacarbazine, 93 % for dabrafenib vs vemurafenib). For dabrafenib vs dacarbazine nearly all of the incremental costs (99.3 %) are drug related costs that occur during PFS whereas for dabrafenib vs vemurafenib incremental costs are divided almost equally between PFS (44.1 %) and PPS (46.3 %). Thus the methods used to estimate PFS, OS and PPS, based on data from the BREAK-3 [17] trial, were considered central to determining the most reliable assessment of cost effectiveness by the ERG. The ERG highlighted that the importance of the large estimated values for PPS gain ascribed to dabrafenib becomes clear from the sensitivity of the company's ICER to alternative assumptions: if only 50 % of the PPS gain in the company'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.

The ERG therefore considered the three phases of the model and the assumptions underlying the modelling of these. First, modelling during the trial period (up to 1.8 years) requires the same three assumptions to hold as described for the ITC to produce valid results. As described above, the ERG did not consider this was the case. In addition, the reliability of the representation of dacarbazine is strongly affected by the efficacy of the assumptions made to support the use of the RPSFTM adjustment. Moreover, the ERG demonstrated that using trial data followed by an exponential extrapolation gave a better fit. Second, the company's model assumes that a log-logistic parameterization of AJCC registry data [8] is appropriate for modelling survival from 1.8 to 10 years. However, no evidence to support the clinical or biological plausibility of this assumption was provided and furthermore, the ERG noted that the AJCC published data [8] relates specifically to a North American as opposed to UK population. During phase 3, the company's model defaults to the use of background mortality rates based on UK life table statistics to represent the experience of all survivors from 10 to 30 years. The ERG noted that this implicitly assumes that long-term survivors are effectively cured of metastatic cancer, a very strong assumption for which no supporting objective evidence was provided by the company. The ERG expressed particular concern about the discontinuities in mortality rates that occurred between phase I and phase 3 (as shown in Figure 1). While such abrupt changes in mortality can occur in clinical trials, they are always the consequence of a significant disease or treatment event, such as the start or termination of treatment, or a serious alteration in a patient's condition. The abrupt changes in mortality rates observed here, however, have no clinical explanation and only relate to convenient choices made for modelling purposes. However, the consequence of these choices is to bias the analysis in favour of dabrafenib and against the comparators, especially dacarbazine.

Finally, the ERG noted that the company has used RPSFTM adjusted data as the basis for modelling OS. The ERG accepted that adjusting for crossover may appear to be a sensible measure, particularly where the treatment that is crossed over to is showing improved efficacy, as appears to be the case from an analysis of OS, PFS and ORR in BREAK-3 [17]. However, the ERG also argued that the assumption requires strong justification since it can radically alter the model estimates of cost effectiveness. In particular, the ERG noted, patients in the dacarbazine arm whose disease has progressed are unlikely to be in a similar physical condition (and therefore have similar survival prognosis) as those starting dabrafenib as first-line

chemotherapy. Hence while treatment crossover may have some efficacy, it is not certain that the recipients will receive 100 % of the efficacy experienced in first-line therapy since those patients suffering early progression are likely to be those with the least propensity to benefit from further treatment. Therefore the ERG requested an analysis of PPS comparing 37 dacarbazine treated patients (69 %) who received subsequent dabrafenib with the 17 patients (31 %) who did not. Despite this being a non-randomized comparison, similar proportions died (70 % and 71 % respectively) and remained in ongoing follow-up at data-cut (24 % and 24 % respectively). The time from disease progression in terms of median (50 % survival), first quartile (75 % survival) and third quartile (25 % survival) are shown in Figure 2 together with confidence intervals. It is apparent that these data offer no convincing evidence of any significant survival difference, and therefore the null hypothesis (that there is no crossover effect favouring dabrafenib) cannot be rejected. This is particularly important since the use of the RPSFTM adjusted survival data from the BREAK-3 [17] trial establishes a large survival difference at the end of the trial data (after 1.8 years). The subsequent use of reduced mortality rates in phases 2 and 3 has the effect of extending the duration of this benefit. The result is that PPS gains are elongated and the ICER per QALY gained for dabrafenib compared with dacarbazine is substantially reduced.

The ERG carried out an analysis to determine the effect of censoring bias. This analysis was done to inform the choice of the most suitable parametric function with which to model BREAK-3 [17] PFS data in order to allow reliable long-term projection of PFS trends. The ERG noted that, for both dabrafenib and dacarbazine, it appears that there is a short period (between 8 and 12 weeks) free of events, followed by a period of high event risk modulated by a regular pattern related to the regular protocol-determined patient assessments. Finally, in both trial arms the cumulative hazard trend settles to a steady near-linear pattern. The ERG therefore concluded that the most appropriate method of representing lifetime PFS trends was to use the 'area under the curve' (AUC) approach to capture PFS in the early variable segment, and then fit a simple linear cumulative hazard trend, equivalent to an exponential projective function for the latter period.

The results are shown in Figure 3 and Figure 4, and compared with both the trial Kaplan-Meier data and the company's log-normal models. It is evident that the company's approach tends to over-estimate the long-term hazard rate (i.e. under-estimate PFS) in both the dabrafenib arm and the dacarbazine arm. This is a result of using the whole data set (including the early

variable phase) for model calibration and the adoption of a common constant proportional hazards assumption.

The ERG's re-analysis of PFS data resulted in an additional 7 to 8 days of PFS gain from use of dabrafenib. Using the ERG PFS estimates in the company's model results in a small increase in the incremental QALYs per patient (+0.16 %). There is, however, a much larger increase in the incremental cost per patient (+6.32 %). This is mainly due to additional days of treatment with dabrafenib. The ERG's alternative projection of OS reduced the estimated OS gain by almost 70 %. Combining all of the ERG's changes results in an ICER of £112,727 per QALY gained for dabrafenib vs dacarbazine.

The ERG did not conduct exploratory analyses to examine the ICER for dabrafenib vs vemurafenib, because the ERG did not believe the results from the ITC were credible for the reasons outlined above.

3.2.2 Evidence Review Group Conclusions on the Submitted Cost effectiveness Evidence

The company has submitted a complex decision model involving important assumptions which the ERG considers lack reliable evidential support. The three-phase survival model generates unexpected and unjustifiable sudden changes in mortality rates which serve only to artificially extend expected patient survival times and thereby exaggerates the apparent post-treatment survival benefit attributed to dabrafenib. Crossover analyses employed by the company are not supported by objective evidence that such crossover has any measurable effect on survival outcomes. Nor are crossover analyses supported by evidence that patients electing for crossover at disease progression to receive dabrafenib are in a similar condition, and therefore have an equivalent propensity to benefit, to those receiving dabrafenib at randomization. Crossover analyses should therefore be considered speculative. Applying the latest OS data from BREAK-3 [17] to a less complex model structure based solely on survival data from this trial reduces the net survival gain by almost 70 %. Applying all additional ERG amendments increases the estimated ICER for dabrafenib compared with dacarbazine from £60,980 to £112,727 per QALY gained. The ERG does not believe assumptions about constant proportional hazards both within and between the two trials used to derive an ITC of dabrafenib to vemurafenib are valid. Therefore results of the comparison of dabrafenib to vemurafenib should not be considered meaningful or reliable.

4 National Institute for Health and Care Excellence Guidance

The AC agreed that the appropriate comparator for this appraisal was vemurafenib. It acknowledged the concerns of the ERG related to the lack of direct evidence to compare the effectiveness of dabrafenib and vemurafenib, the significant limitations of the ITC provided by the company and the numerous uncertainties related to the assumptions related to survival in the economic model provided by the company.

In addition to the evidence presented by the company and critiqued by the ERG, the AC took into account the views of a patient expert and clinical specialist. The patient expert highlighted that metastatic melanoma can be associated with severe and debilitating symptoms and dabrafenib may sometimes have very rapid therapeutic effects such as improving poor performance status and slowing down the progression of high volume disease, even in those who are severely ill or bed-ridden. The clinical specialist stated that in clinical practice, the effectiveness of dabrafenib and vemurafenib were not considered to differ. Hence the choice between the two treatments would be largely based on their adverse reaction profiles. The clinical specialist explained that compared to vemurafenib there were much lower rates of photosensitivity (which may be a major problem for some patients) but higher rates of non-specific fever.

With regard to possible differences between the key trials, the AC also heard from the clinical specialist that although LDH level is one of many measures of disease severity used in clinical practice, it was not a marker of disease prognosis that could be relied on in isolation. Taking into account the evidence also presented by the company, the AC concluded that compared with dacarbazine, dabrafenib significantly improved PFS and '*probably improved*' OS [29], noting that BRIM-3 [18] was a large trial and could show an OS benefit with vemurafenib, whereas BREAK-3 [17] was a smaller trial and it would be more difficult to demonstrate a statistically significant OS benefit with dabrafenib. The AC was therefore unable to draw firm conclusion about the magnitude of overall survival benefit. In spite of limitations in the data comparing dabrafenib to vemurafenib, the AC took the view that the two drugs were *'likely'* of similar clinical effectiveness and since the overall costs were similar, the use of dabrafenib should be recommended in this patient population [29]. The AC therefore reached the following decision: *'Dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the company provides dabrafenib with the discount agreed in the patient access scheme'* [29].

5 Conclusion

A clinical benefit of dabrafenib vs dacarbazine in terms of PFS has been demonstrated from BREAK-3 [17]. Significant benefits of vemurafenib vs dacarbazine in terms of PFS and OS have been demonstrated in BRIM-3 [18]. Vemurafenib is now the standard of care in clinical practice and hence it was important to compare dabrafenib to vemurafenib. In the absence of direct head-to-head evidence of these two drugs, the company conducted an ITC. The ERG noted key assumptions underpinning the conduct of the ITC did not hold and therefore put in question the validity of the clinical and cost effectiveness evidence derived from the ITC. Furthermore, with regard to cost effectiveness, the ERG noted the model suggested extensive PPS unsubstantiated by the existing data, clinical experience or even logical thought.

The AC acknowledged the limitations with the evidence base highlighted by the ERG. However, it nevertheless concluded: *'that there was no clear evidence that dabrafenib and vemurafenib differed in clinical effectiveness and that it would not be unreasonable to assume that they have similar effect'* [29]. Furthermore: *'the overall costs were not different in the economic analysis … [and so] any difference in the cost effectiveness would be small and would fall within the range considered to be a cost effective use of NHS resources'* [29]. Hence, the use of dabrafenib was recommended for treating unresectable or metastatic BRAF V600 mutation-positive melanoma.

Acknowledgements

This project was funded by the National Institute for Health Research Health Technology Assessment Programme (project number 12/54). See the Health Technology Assessment programme website for further project information. www.hta.ac.uk.

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the National Institute for Health and Care Excellence or the Department of Health.

The authors have no competing interests

Contributions of authors:

Nigel Fleeman: Project lead, drafted clinical results section and supervised the final report

Adrian Bagust: Critical appraisal of the economic model

Sophie Beale: Critical appraisal of the economic evidence

Angela Boland: Summary and critical appraisal of the clinical and economic evidence

Marty Richardson: Critical appraisal of clinical statistical approach

Kerry Dwan: Critical appraisal of clinical statistical approach

Rumona Dickson: Summary and critical appraisal of the clinical evidence

Yenal Dundar: Cross checking of company's search strategies

Helen Davis: Critical appraisal of the company's submission

Lindsay Banks: Critical appraisal of the company's submission

References

1. National Institute for Health and Clinical Excellence (NICE). Guide to the single technology appraisal process. 2009. http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Guide-to-the-single-technology-appraisal-process.pdf. Accessed 12 Nov 2014.

2. National Institute for Health and Care Excellence. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation‐positive melanoma. 2014. https://www.nice.org.uk/guidance/TA321. Accessed 5 June 2014.

3. Cancer Research UK. Skin Cancer statistics - UK. 2011. http://info.cancerresearchuk.org/cancerstats/types/skin/. Accessed 12 Nov 2014.

4. Lacy KE, Karagiannis SN, Nestle FO. Advances in the treatment of melanoma. Clin Med. 2012;12(2):168-71.

5. Long G, Menzies A, Nagrial A, Haydu L, Hamilton A, Mann G et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol. 2011;29(10):1239-46.

6. Francken AB, Accortt NA, Shaw HM, Wiener M, Soong SJ, Hoekstra HJ et al. Prognosis and determinants of outcome following locoregional or distant recurrence in patients with cutaneous melanoma. Ann Surg Oncol. 2008;15(5):1476-84.

7. Reed KB, Cook-Norris RH, Brewer JD. The cutaneous manifestations of metastatic malignant melanoma. Int J Dermatol. 2012;51(3):243-9.

8. Balch C, Gershenwald J, Soong S, Thompson J, Atkins M, Byrd D et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27(36):6199-206.

9. Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Spatz A et al. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline - Update 2012. Eur J Cancer. 2012;48:2375-90.

10. Dickson R, Boland A, Bagust A, Blundell M, Massey G, Dundar Y et al. Ipilimumab for previously treated unresectable malignant melanoma: A Single Technology Appraisal. 2011. https://www.nice.org.uk/guidance/ta268/documents/melanoma-stage-iii-or-iv-ipilimumab-evidence-review-group-report3. Accessed 12 Nov 2014.

11. GlaxoSmithKline UK. Melanoma (unresectable/metastatic $BRAF^{V600}$ mutation positive) - dabrafenib. Manufacturer's Submission to NICE Appraisal Process. . 2014. https://www.nice.org.uk/guidance/ta321/documents/melanoma-braf-v600-unresectable-metastatic-dabrafenib-id605-evaluation-report2. Accessed 12 Nov 2014.

12. National Institute for Health and Clinical Excellence. Vemurafenib for the treatment of unresectable locally advanced or metastatic $BRAF^{V600}$ mutation-positive malignant melanoma 2011. http://www.nice.org.uk/guidance/ta269/resources/guidance-vemurafenib-for-treating-locally-advanced-or-metastatic-brafv600-mutationpositive-malignant-melanoma-pdf. Accessed 12 Nov 2014.

13. National Institute for Health and Clinical Excellence. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. 2012. https://www.nice.org.uk/guidance/ta268. Accessed 12 Nov 2014.

14. National Institute for Health and Care Excellence. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma [TA319]. https://www.nice.org.uk/guidance/TA319. Accessed 12 Nov 2014.

15. European Medicines Agency. Tafinlar(dabrafenib) EPAR summary for the public 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002604/WC500149674.pdf. Accessed 12 Nov 2014.

16. Fleeman N, A B, Beale S, Boland A, Dickson R, Richardson M et al. Dabrafenib for the treatment of unresectable, advanced or metastatic BRAFv600 mutation-positive melanoma[ID605]: A Single Technology Appraisal. 2014. http://www.nice.org.uk/guidance/ta321/documents/melanoma-braf-v600-unresectable-metastatic-dabrafenib-id605-evaluation-report2. Accessed 12 Nov 2014.

17. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M et al. Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358-65.

18. McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R et al. Safety and efficacy of vemurafenib in $BRAF^{V600E}$ and $BRAFV^{600K}$ mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014;15(3):323-32.

19. GlaxoSmithKline. A Phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma (CSR). 2011. p. 1-1768.

20. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J et al. Combined BRAF and MEK inhibition in melanoma with $BRAF^{V600}$ mutations. N Engl J Med. 2012;367(18):1694-703. doi:10.1056/NEJMoa1210093.

21. GlaxoSmithKline. NCT01584648: A Study Comparing Trametinib and Dabrafenib Combination Therapy to Dabrafenib Monotherapy in Subjects With BRAF-mutant Melanoma. http://clinicaltrials.gov/show/NCT01584648. Accessed 3 June 2014.

22. Ascierto PA, Minor D, Ribas A, Lebbe C, O'Hagan A, Arya N et al. Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. J Clin Oncol. 2013;31(26):3205-11.

23. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): A multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(11):1087-95.

24. Bucher H, Guyatt G, Griffith L, Walter S. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1991;50(6):683-91.

25. McArthur G, Hauschild A, Robert C, Haanen JB, Ascierto P, Lee RJ et al. Vemurafenib improves overall survival compared to dacarbazine in advanced $BRAF^{V600E}$-mutated melanoma: Updated survival results from a phase III randomised, open-label, multicentre trial. Eur J Cancer. 2011;47:14.

26. Gray MR, Martin del Campo S, Zhang X, Zhang H, Souza FF, Carson WE, 3rd et al. Metastatic melanoma: lactate dehydrogenase levels and CT imaging findings of tumor devascularization allow accurate prediction of survival in patients treated with bevacizumab. Radiology. 2014;270(2):425-34.

27. Roche. Roche response to first ACD (7 July 2012). http://www.nice.org.uk/guidance/ta269/resources/melanoma-braf-v600-mutation-positive-unresectable-metastatic-vemurafenib-roche-products2. Accessed: 2 July 2014.

28. Heron Evidence Development. Systematic review in metastatic malignant melanoma, Version 2.0. 2014.

29. National Institute for Health and Care Excellence. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation‐positive melanoma. NICE technology appraisal guidance 321. 2014. https://www.nice.org.uk/guidance/ta321/resources/guidance-dabrafenib-for-treating-unresectable-or-metastatic-brafv600-mutationpositive-melanoma-pdf. Accessed 5 Jan 2015.

Tables and figures

Table 1: Results of individual trials and inputs for the direct and indirect treatment comparisons

Outcome	BREAK-3 [17] PFS data-cut: June 2012 OS data-cut: December 2012		BRIM-3 [18] PFS and OS data-cut: February 2012	
	Dabrafenib (N=187)	Dacarbazine (N =63)	Vemurafenib (n=337)	Dacarbazine (N=338)
Investigator assessed median PFS months (95 % CI)	6.9 (5.2 to 9.0)	2.7 (1.5 to 3.2)	6.9 (6.1 to 7.0)	1.6 (1.6 to 2.1)
ITT PFS HR (95 % CI); p-value	0.37 (0.24 to 0.58); p<0.0001		0.38 (0.32 to 0.46); p<0·0001	
Median OS months (95 % CI)	18.2 (16.6 to NR)	15.6 (12.7 to NR)	13.6 (12.0 to 15.2)	10.3 (9.1 to 12.8)
Unadjusted OS HR (95 % CI)	0.76 (0.49 to 1.18)[a]		0.76 (0.63 to 0.93)[a]	
RPSFTM adjusted HR (95 % CI)	0.55 (0.21 to 1.43)[b]		0.64 (0.53 to 0.78)[b]	
ORR % (95 % CI)	59 (51.4 to 66.0)	24 (14.0 to 36.2)	57[c]	8.6[c]

This table is adapted from Table 8 of Fleeman et al [16] (Crown copyright)

CI confidence interval, *HR* hazard ratio, *ITT* intention to treat, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *RPSFTM* Rank Preserving Structural Failure Time Model

a Data input into the company's modified ITC at the request of the ERG
b Data input into the company's original ITC
c Only limited data for BRIM-3 was reported in the company's submission (ORR % for vemurafenib arm reported in the text only with no CIs), the data for dacarbazine are therefore taken from the published paper for BRIM-3 [18]; it should also be noted that the data for BRIM-3 are confirmed by independent review whereas in BREAK-3, the investigator assessed ORR are reported

Table 2: Results of indirect treatment comparison

Outcome	Treatment	Control	HR	95 % CI	
				Lower	Upper
PFS	Dabrafenib	Vemurafenib	0.97	0.59	1.60
RPSFTM adjusted OS	Dabrafenib	Vemurafenib	0.86	0.32	2.29
Unadjusted OS	Dabrafenib	Vemurafenib	1.00	0.62	1.62

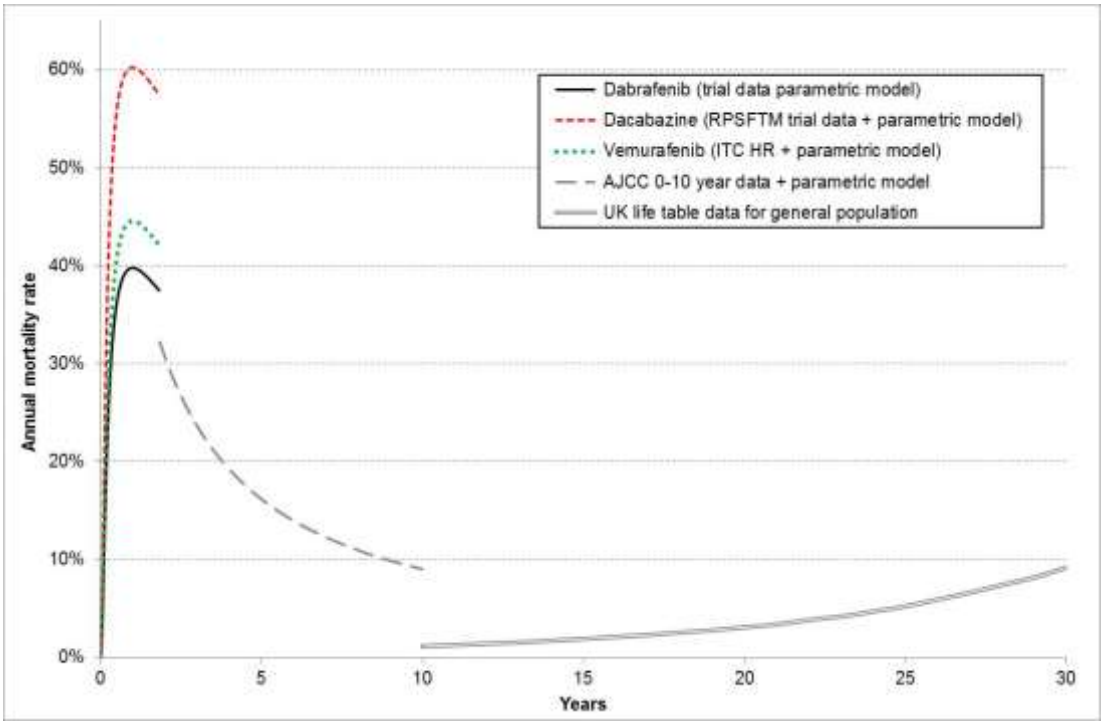
This table is adapted from Table 10 and Table 11 of Fleeman et al [16] (Crown copyright)

CI confidence interval, *HR* hazard ratio, *OS* overall survival, *PFS* progression-free survival, *RPSFTM* Rank Preserving Structural Failure Time Model

Table 3: Type of first systemic therapy received on disease progression in BREAK-3

Sytemic therapy	Dabrafenib	Dacarbazine
Dabrafenib	37 (59 %)*	38 (20 %)
Ipilimumab	2 (3 %)	25 (13 %)
Dacarbazine	2 (3 %)	16 (9 %)
Vemurafenib	6 (10 %)	9 (5 %)
Fotemustine	1 (2 %)	4 (2 %)
Lenvatinib mesilate	0	4 (2 %)
Carboplatin/paclitaxel	0	3 (2 %)
Interleukin-2	0	2 (1 %)
Temozolomide	1 (2 %)	1 (<1 %)
Mitogen-activated protein / extracellular signal-regulated kinase (nos)	0	1 (<1 %)
Pembrolizumab	0	1 (<1 %)

This table is adapted from data presented by the company as part of its factual error check of the ERG report (Crown copyright)
* 36 (57 %) of patients were considered to have crossed-over by the company



AJCC American Joint Committee on Cancer, *HR* hazard ratio, *ITC* indirect treatment comparison, *RPSFTM* Rank preserving structural time failure model, *UK* United Kingdom

Figure 1 Mortality rates in the company's base case analysis

This figure is taken from Figure 5 of Fleeman et al [16] (Crown copyright)

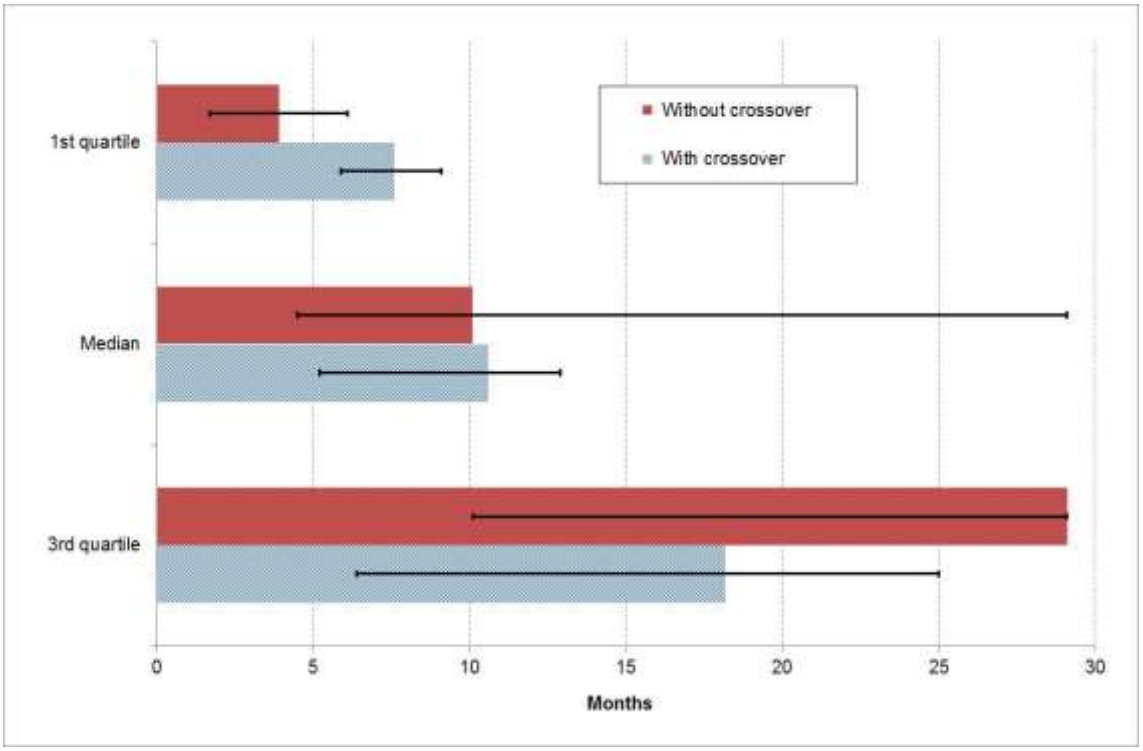


Figure 2 Post-progression survival comparing dacarbazine patients who did and did not crossover to dabrafenib on disease progression

This figure is taken from Figure 6 of Fleeman et al [16] (Crown copyright)

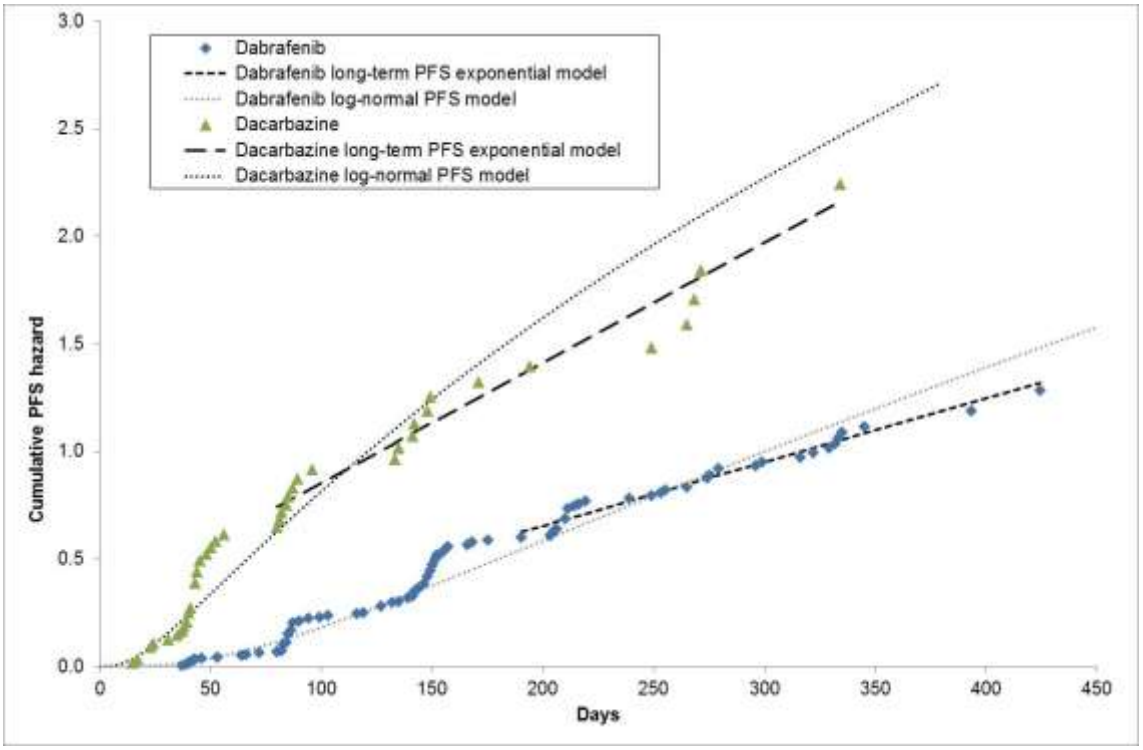


Figure 3 BREAK-3 cumulative hazard Kaplan-Meier PFS data, ERG long-term linear trends and the company's log-normal models

This figure is taken from Figure 14 of Fleeman et al [16] (Crown copyright)

ERG evidence review group, *PFS* progression-free survival

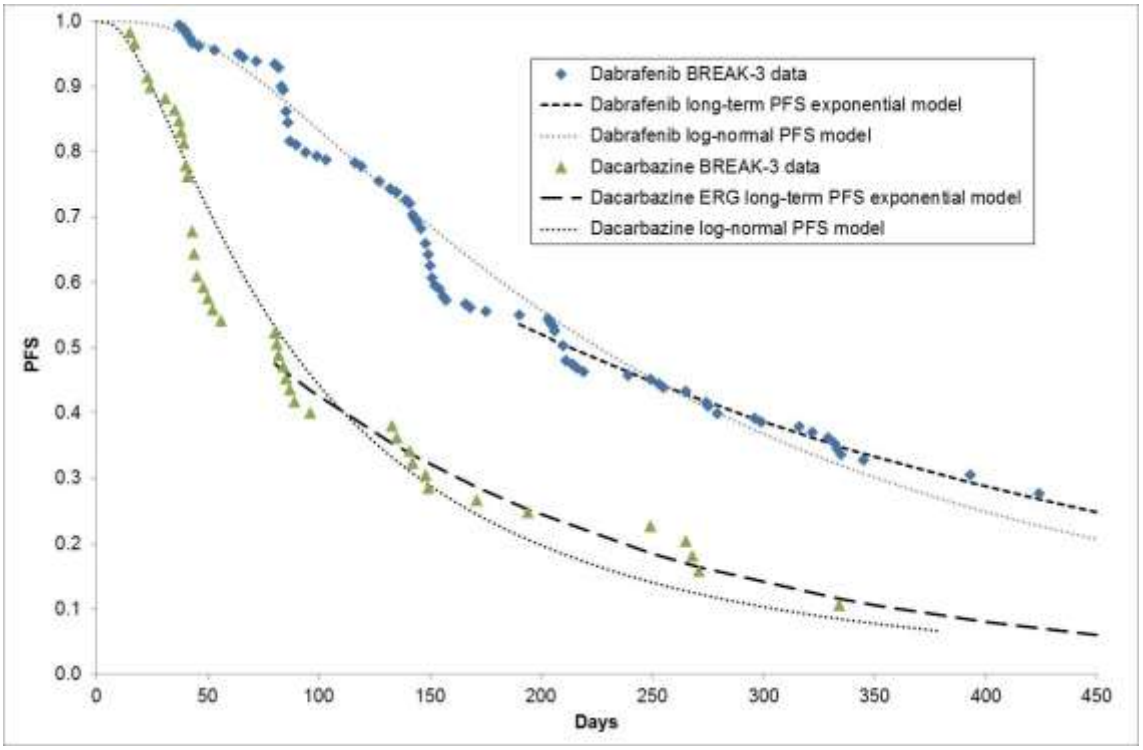


Figure 4 BREAK-3 Kaplan-Meier PFS data, ERG long-term exponential models and the company's log-normal models

This figure is taken from Figure 15 of Fleeman et al [16] (Crown copyright)

ERG evidence review group, *PFS* progression-free survival