NICE National Institute for Health and Care Excellence

NICE guidance

Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

This guidance was developed using the single technology appraisal (STA) process.

1.1 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.

2 The technology

2.1 Dabrafenib (Tafinlar, Novartis) is an inhibitor of the BRAF V600 protein kinase. When the activity of protein kinase is blocked, the cancer cells stop growing and die. Dabrafenib has a marketing authorisation in the UK in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

2.2 The summary of product characteristics lists the following very common adverse reactions for dabrafenib: papilloma, decreased appetite, headache, cough, nausea, vomiting, diarrhoea, hyperkeratosis, alopecia, rash, palmar-plantar erythrodysaesthesia syndrome, arthralgia, myalgia, pain in extremity, pyrexia, fatigue, chills and asthenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price of dabrafenib is £1,400 for a pack of 75-mg capsules (28 capsules per pack) and £933.33 for a pack of 50-mg capsules (28 capsules per pack) (excluding VAT; BNF edition 67). It is taken orally at a recommended dose of 150 mg twice daily. Novartis has agreed a patient access scheme with the Department of Health that makes dabrafenib available with a discount applied at the point of purchase or invoice. The size of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

3.1 The appraisal committee (section 6) considered evidence submitted by the company that manufactures dabrafenib and a review of this submission by the evidence review group (ERG; section 7).

Clinical effectiveness

3.2 The key clinical evidence came from the BREAK-3 trial. This was an international, multi-centre, randomised, open-label, active-controlled trial comparing dabrafenib with dacarbazine in people with previously untreated, unresectable, advanced or metastatic BRAF V600 mutation-positive melanoma. The company also provided supportive evidence from 4 other trials of dabrafenib, including 2 randomised-controlled trials (BRF113220 and Combi-d) and 2 single arm trials (BREAK-2 and BREAK-MB). However, none of these trials included comparators relevant to the decision problem; therefore they were not included in a quantitative analysis.

3.3 Patients in BREAK-3 were randomly assigned in a 3:1 ratio to receive either 150 mg of dabrafenib twice daily orally (n=187) or 1,000 mg/m^2 of body-surface area of dacarbazine by intravenous infusion every 3 weeks (n=63). Baseline patient characteristics were generally similar between the treatment groups. The mean age was 53.5 years in the dabrafenib arm of the trial and 51.6 years in the dacarbazine arm. Approximately 67% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. The company stated that most patients had undergone surgery previously, and adjuvant immunotherapy with interferon was the most common previous anti-cancer therapy.

3.4 The company conducted 2 separate analyses based on 2 different cut-off dates (December 2011 and June 2012) for the primary outcome of investigator-assessed progression-free survival and all secondary outcomes. For the outcome of overall survival, the company conducted a third analysis based on a later cut-off date of December 2012. In response to a request for clarification from NICE, the company presented more recent overall survival data with a

cut-off date of January 2014.

3.5 Results from the June 2012 analysis of BREAK-3 showed that there was a 63% reduction in disease progression for patients receiving dabrafenib compared with patients receiving dacarbazine. The median progression-free survival was 6.9 months for dabrafenib compared with 2.7 months for dacarbazine, a statistically significant difference of 4.2 months (hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.24 to 0.58, p<0.0001). The company reported results from a range of pre-specified subgroups including age, sex, ECOG performance status, disease stage, lactate dehydrogenase levels and number of disease sites. The results showed that the progression-free survival benefit with dabrafenib treatment was generally maintained across each subgroup.

3.6 Results from the December 2012 analysis of BREAK-3 showed an improvement of 2.6 months in the key secondary outcome of median overall survival, which was 18.2 months in the dabrafenib group compared with 15.6 months in the dacarbazine group. However, the difference between the treatments was not statistically significant (HR 0.76, 95% CI 0.48 to 1.21, p value not presented).The company explained that approximately 57% of patients assigned to receive dacarbazine had crossed over to the dabrafenib arm by the time the analysis was conducted in December 2012. Therefore, the company adjusted the overall survival results using the 'rank preserving structural failure time' (RPSFT) model. The RPSFT-adjusted analysis resulted in a hazard ratio of 0.55 (95% CI 0.21 to 1.43). The analysis based on the January 2014 data was not adjusted for crossover, and the results were designated academic in confidence by the company. The company specified that a crossover-adjusted analysis of the final data from BREAK-3 would be completed at a later date.

3.7 Health-related quality of life (HRQoL) was assessed in BREAK-3 using the EuroQoL (EQ-5D) utility index. EQ-5D data were collected for all the participants in the trial at screening, week 6, week 12, week 15, at disease progression, and approximately 30 days after disease progression. The mean change in EQ-5D utility index score from baseline to week 15 was lower in the dabrafenib group (+0.053) than in the dacarbazine group (+0.128).

3.8 The data from December 2012 showed that the most commonly reported grade 3 adverse events with dabrafenib were pyrexia, back pain, squamous cell

carcinoma and hyperglycaemia; whereas neutropenia, decreased appetite and leukopenia had a higher incidence in the dacarbazine arm. Treatment-related adverse events, adverse events leading to discontinuation of trial treatment, and adverse events leading to dose reduction or interruption were not reported for the December 2012 analysis. For the December 2011 analysis, treatment-related adverse events occurred with a higher frequency in the dabrafenib arm (88%) than in the dacarbazine arm (73%), whereas the incidence of adverse events leading to discontinuation of trial treatment or dose reduction was similar between the treatment arms.

Indirect treatment comparison

3.9 To estimate the effectiveness of dabrafenib compared with vemurafenib, in the absence of head-to-head trials comparing dabrafenib and vemurafenib, the company conducted an indirect treatment comparison using data from the BREAK-3 and BRIM-3 trials. BRIM-3 was a multicentre, randomised, open label, active-controlled trial that compared vemurafenib (960 mg twice daily orally; n=337) with dacarbazine (1,000 mg/m^2 of body surface area; n=338). The study population comprised adults with previously untreated advanced or metastatic BRAF V600 mutation-positive melanoma. Patients in BRIM-3 were similar to those in BREAK-3 in terms of age, sex, ECOG status and disease stage. However, the trials differed in the proportion of patients with elevated lactate dehydrogenase levels (BREAK-3 = 34%; BRIM-3 = 58%), sample size (BREAK-3, n=250; BRIM-3, n=675), ratio of randomisation (BREAK-3, 3:1; BRIM-3, 1:1) and median follow-up time at the latest cut-off points.

3.10 Overall survival and progression-free survival were joint primary outcomes in BRIM-3. The company explained that approximately 34% of patients assigned to receive dacarbazine had crossed over to the vemurafenib arm by the time the analysis was conducted at the latest cut-off date (February 2012). The RPSFT method was used to adjust for crossover. The results using the February 2012 data showed statistically significant differences between vemurafenib and dacarbazine for the primary outcomes of progression-free survival (HR 0.38, 95% CI 0.32 to 0.46, p<0.001); unadjusted overall survival (HR 0.76, 95% CI 0.63 to 0.93, p value not presented) and RPSFT-adjusted overall survival (HR 0.64, 95% CI 0.53 to 0.78, p value not presented).

3.11 The company conducted the indirect comparison using the method described by Bucher et al. based on the assumption that the patient characteristics between BREAK-3 and BRIM-3 were similar. Results of the indirect comparison found no difference between dabrafenib and vemurafenib in progression-free survival (HR 0.97, 95% CI 0.59 to 1.60) or overall survival (unadjusted HR 1.00, 95% CI 0.62 to 1.62; crossover-adjusted HR 0.86, 95% CI 0.32 to 2.29).

Cost effectiveness

3.12 The company submitted a de novo '3-state partitioned survival' model comparing dabrafenib with dacarbazine and vemurafenib for previously untreated, unresectable or metastatic BRAF V600 mutation-positive melanoma. The company considered a partitioned survival model to be more appropriate than a Markov model because it uses distributions of progression-free survival and overall survival as model inputs and therefore ensures that the model results match those observed in the trial. Patients were assumed to enter the model in the 'progression-free' health state, and in each cycle could either remain in that state or progress to a worse state; that is, the 'post-progression' health state or 'death' state. The model had a lifetime horizon of 30 years, consisting of weekly cycles and no half-cycle correction. The company based the analysis on an NHS and personal social services perspective, and costs and benefits were discounted at an annual rate of 3.5%. The company explained that there were not enough clinical data available for it to estimate the cost effectiveness of dabrafenib in adults who had received previous treatment. No subgroup analyses were conducted by the company.

3.13 For the comparison with dacarbazine, the proportion of people in each health state in the company's model was estimated based on survival functions for investigator-assessed progression-free survival and overall survival using the June 2012 and December 2012 data respectively from BREAK-3. The company fitted independent log-normal distributions to individual patient data for progression-free survival for both treatment arms from time 0, using accelerated failure time (AFT) regression. The fitted curves were then extrapolated beyond the trial period (defined as 53.1 weeks for dacarbazine and 71.1 weeks for dabrafenib based on the last censor or observed failure time for progression-free survival) to 30 years. The company stated that the log-normal distribution

provided the best fit to the data based on goodness-of-fit statistics and comparisons of the area under the curve.

3.14 The company modelled overall survival in the dabrafenib arm in 3 phases:

- Phase 1: The company fitted the log-normal distribution to individual patient data from the dabrafenib arm of BREAK-3 for the trial period only (defined as 96 weeks based on maximum censor or failure time for overall survival) using AFT regression.
- Phase 2: From the end of trial follow-up and up to 10 years, the company applied hazard rates obtained by fitting the log-logistic distribution to the overall survival data from the American Joint Committee on Cancer (AJCC) registry reported by Balch et al. (2009), which was weighted by the relative proportions of patients according to disease stage in BREAK-3.
- Phase 3: For the remaining duration of the model, the company modelled survival by applying mortality rates obtained from UK general population life tables.

3.15 The company stated that there are uncertainties associated with fitting parametric curves to the data from the RPSFT analysis for the dacarbazine arm because of the small number of patient in the analysis. Therefore, it modelled overall survival for the dacarbazine arm as proportional hazards compared with dabrafenib using the RPSFT-adjusted hazard ratio from BREAK-3. This hazard ratio was applied for the trial period of 96 weeks, after which no further treatment effect was assumed.

3.16 For the comparison with vemurafenib, the company applied the progression-free survival and overall survival hazard ratios from the indirect treatment comparison to the parametric survival curves used to model the dabrafenib arm. Proportional hazards were assumed throughout the entire model timeframe for progression-free survival, whereas for overall survival it was assumed for the trial period of 96 weeks only.

3.17 Treatment-specific EQ-5D utility data for pre-progression and post-progression, derived directly from BREAK-3, were used in the model for dabrafenib and dacarbazine. The utility values for the progression-free health state were 0.77 for

dabrafenib and 0.75 for dacarbazine. The value for the post-progression state was 0.68 for dabrafenib. The company did not calculate the decrement in post-progression utility for dacarbazine because of potential confounding from crossover in BREAK-3. Given that there was no rationale to assume that health-related quality of life after progression would differ between treatments, the company assumed that the post-progression utility value for dacarbazine would be the same as that for dabrafenib. In the absence of comparable EQ-5D utility data for vemurafenib, the company assumed that the vemurafenib utility values would be the same as those for dabrafenib. The company did not include disutilities associated with adverse events in the model because it considered the effect of adverse events on quality of life to be captured in the progression-free and post-progression health state utility values. Health related quality of life was assumed to be constant over time in each health state.

3.18 Costs incorporated in the company's model included drug costs, dispensing costs for dabrafenib and vemurafenib, administration cost for dacarbazine, BRAF testing, anti-cancer therapy after the study, costs associated with health states and adverse events and one-off costs for starting treatment and for death. The costs of dabrafenib and vemurafenib were estimated using the patient access schemes provided by the companies; the cost of dacarbazine was based on the list price. Estimates of the costs of treating adverse events were based on the results of a cost-of-illness study commissioned by the company and the incidence of adverse events from BREAK-3 and BRIM-3. The anti-cancer therapy costs after the study were estimated to be £3,013 for dabrafenib and vemurafenib and £6,044 for dacarbazine.

3.19 The base-case incremental cost-effectiveness ratio (ICER) was £49,019 per quality-adjusted life year (QALY) gained for dabrafenib compared with dacarbazine, and £11,028 per QALY gained for dabrafenib compared with vemurafenib.

3.20 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. At a maximum acceptable ICER of £50,000 per QALY dabrafenib would have a 43.5% probability of being cost effective compared with dacarbazine.

3.21 The company conducted a series of deterministic sensitivity analyses. For the comparison with dacarbazine, overall survival was the key driver of the cost-effectiveness results. When the RPSFT-adjusted hazard ratio for overall survival was varied using the 95% confidence interval, the ICERs ranged from £26,470 per QALY gained to dacarbazine dominating dabrafenib (that is, dabrafenib was more expensive and less effective). The key driver of the cost-effectiveness result for the comparison with vemurafenib was the progression-free survival assumption; varying the hazard ratio using the 95% confidence interval resulted in ICERs ranging from £67,220 per QALY gained to a scenario where dabrafenib dominated vemurafenib. The cost effectiveness estimate for dabrafenib compared with vemurafenib was also sensitive to the overall survival hazard ratio used in the model, assuming a class effect between dabrafenib and vemurafenib and using alternative distributions to model survival. Changes to the time horizon, cost parameters and utility values did not have a large effect on the base-case ICER.

Evidence review group comments

3.22 The ERG was satisfied that all relevant studies with the appropriate comparisons were included in the company's analysis. In general, it concluded that BREAK-3 was a good quality trial. The ERG agreed that evidence from the BREAK-3 trial shows that treatment with dabrafenib was associated with progression-free survival benefits compared with dacarbazine. However, it did not agree with the company that crossover in BREAK-3 explained the lack of an overall survival benefit with dabrafenib, because an analysis of the survival data showed that patients in the dacarbazine arm who crossed over did not gain any significant benefit over patients that did not cross over.

3.23 The ERG did not consider the RPSFT method used to adjust for cross-over in BREAK-3 to be appropriate for the following reasons:

- survival data was not based on the final trial data, but on an interim analysis with few deaths
- the assumption in the RPSFT method of a 'common treatment effect' (that is, that the effect of dabrafenib is the same whether treatment starts at

diagnosis or after the disease has progressed) is questionable

- patients in the dabrafenib arm and dacarbazine arm did not receive similar treatments at the time of disease progression, and some received treatments that are not used in routine clinical practice in the UK.

  The ERG stated that it might have been more appropriate to use the 'inverse probability of censoring weighting' (IPCW) method to adjust for crossover. However, it acknowledged that the lack of complete overall survival data and the small number of deaths to date may invalidate the use of the IPCW method at present.

3.24 Regarding the company's indirect treatment comparison, the ERG was satisfied that the BREAK-3 and BRIM-3 trials were broadly similar in terms of patient population and eligibility criteria. However, it noted that a greater proportion of patients in BRIM-3 had lactate dehydrogenase levels above the upper limit of the normal range than patients in BREAK-3. The ERG commented that this may have a negative effect on the prognosis of patients in BRIM-3 compared with that for patients in BREAK-3. The ERG questioned the validity of the approach used to conduct the indirect comparison because the assumption about constant hazard ratios for progression-free survival and overall survival within BREAK-3 and the assumption about constant proportional hazards for dacarbazine overall survival between the 2 trials were not met. The ERG also commented that because of the problem of adjusting for crossover in the individual trials it is more appropriate to use the unadjusted hazard ratios in the indirect treatment comparison. The ERG also noted that the most recent overall survival data from BREAK-3 trial (January 2014 data) had not been used in the company's indirect treatment comparison. In view of these issues, the ERG stated that the evidence from the company's indirect treatment comparison was not robust. It was therefore unable to comment on the clinical effectiveness of dabrafenib compared with vemurafenib.

3.25 The ERG stated that the assumptions about the clinical effectiveness model inputs were the main drivers of the company's cost effectiveness estimate. The ERG noted that the company censored progression-free and overall survival data at the date of last observation, which could misrepresent survival projections when used to calibrate parametric survival functions. It considered that, to remove any bias, censoring survival data at the date of data-cut would have been

more appropriate.

3.26 The ERG noted that the company modelled overall survival in 3 phases and it considered this approach to be complex and associated with several limitations, as follows:

- Phase 1 from randomisation until 96 weeks (1.8 years): The ERG stated that the log normal distribution used to represent the whole period of the trial follow-up was questionable because the log-normal distribution is known to have a long tail, and therefore overestimates overall survival gain. The ERG also considered that it would have been more appropriate to use the most recent overall survival data available from BREAK-3 (January 2014).
- Phase 2 data from 1.8 to 10 years: The ERG noted that the company did not present evidence to support the clinical or biological plausibility of the log-logistic distribution fitted to the AJCC registry data used in this phase. It also noted that the registry data are based on a North American population and therefore may not be representative of the UK population.
- Phase 3 data from 10 to 30 years: The ERG noted that this approach assumes, without any supporting evidence, that long-term survivors are effectively cured of metastatic disease.

3.27 The ERG noted that the dabrafenib parametric model was used as a basis for modelling survival for the first 10 years in the dacarbazine and vemurafenib arms and was concerned that the company's assumption of proportional hazards across the 3 treatments may not be valid. The ERG indicated that the reliability of this approach was strongly affected by the assumptions about the RPSFT-adjusted hazard ratio from BREAK-3 used to model the dacarbazine arm.

3.28 The ERG noted that the majority of the estimated QALY gain in the company's model arises from the estimated life-years after disease progression (62% for the comparison with dacarbazine and 93% for the comparison with vemurafenib). It also noted that the estimated mean survival in the company's model is much larger than is normally observed in clinical trials or in registry data. The ERG explained that 2 aspects of the model contributed to these results:

- the use of the RPSFT-adjusted survival data from BREAK-3 resulted in a large survival difference between dabrafenib and dacarbazine after 96 months

- the structure of the model in 3 phases involves applying mortality rates from different sources that are not compatible, and that seriously underestimate death rates, so extending estimated survival times over many years. The ERG drew attention to the sudden changes in mortality rates at 96 months and 10 years in the company's model, which lack any clinical or epidemiological justification.

  These 2 features of the model serve to establish a large early survival advantage for dabrafenib at 96 months, which is then extended over 3 decades by the overoptimistic modelling of mortality.

3.29 The ERG noted that a comparison of the cost effectiveness of dabrafenib and vemurafenib depends on an indirect treatment comparison between the BREAK-3 and BRIM-3 trials, in order to generate progression-free survival and overall survival hazard ratios. The ERG examined the trial results and found that the proportional hazards ratio assumption was not valid within each trial or between the dacarbazine arms of the trials. Therefore, robust hazard ratios for dabrafenib compared with dacarbazine could not be obtained. The ERG concluded that any estimated ICERs generated by this indirect comparison would be unreliable and likely to be misleading. The ERG therefore restricted any detailed numerical comparisons to the direct evidence from the BREAK-3 trial for dabrafenib compared with dacarbazine.

3.30 For the comparison with dacarbazine, the ERG used alternative methods to derive the clinical effectiveness model inputs. The ERG revised the censoring of progression-free survival data for some patients still at risk at the end of the trial to reflect the date of data-cut rather than the date of last observation. It then used the area under the curve approach to model progression-free survival in the early variable segment and an exponential projective function for the latter period. This change increased the ICER from £49,019 to £52,035 per QALY gained.

3.31 The ERG analysed the latest overall survival data from the January 2014 data and concluded that the risk of bias introduced by the choice of censoring method is small, and could only possibly affect the last few recorded events in each trial arm. Therefore the analysis was carried out without any post-hoc adjustments. The ERG was aware that the latest overall survival data were unadjusted for cross

over. However, it noted its earlier analysis, which showed no statistically significant survival difference between the patients in the dacarbazine group who crossed over and those who did not cross over (see section 3.21). The ERG then modelled overall survival using the area under the curve survival data until a long term trend was established and then applying the long-term exponential function throughout the rest of the trial period, that is, 1.8 years. It continued to apply the long-term exponential projection derived from BREAK-3 data throughout the company's phase 2 time period, that is, up to 10 years. The ERG noted that all patients had died at the end of 10 years; therefore it restricted the modelling to 10 years rather than the 30 years assumed by the company. The ERG's analysis resulted in a considerably lower overall survival gain than the company's base case, and the resulting ICER was £99,560 per QALY gained.

3.32 The ERG made several amendments to the dacarbazine acquisition and administration cost estimates, which increased the ICER for dabrafenib compared with dacarbazine by £87 per QALY gained. The ERG applied equal costs for anti-cancer treatment after the study to the dabrafenib and dacarbazine groups because the difference between the post-study treatments received in BREAK-3 were not statistically significant. This amendment increased the ICER by £3,047 per QALY gained for dabrafenib compared with dacarbazine. Combining all the ERG's exploratory analyses and model amendments resulted in an ICER of £112,727 per QALY gained for the comparison with dacarbazine.

3.33 Full details of all the evidence are in the committee papers.

4 Consideration of the evidence

The appraisal committee reviewed the data available on the clinical and cost effectiveness of dabrafenib, having considered evidence on the nature of unresectable or metastatic BRAF V600 mutation-positive melanoma and the value placed on the benefits of dabrafenib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.1 The committee considered the clinical need for treatment in people with unresectable or metastatic BRAF V600 mutation-positive melanoma. The committee heard from the patient expert that metastatic melanoma can be associated with severe and debilitating symptoms. 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. In some cases, this enables people to resume everyday tasks and activities. The patient expert also stated that people may experience very few side effects with dabrafenib. The clinical specialist explained that the side-effect profile of dabrafenib differed from that of vemurafenib in that there were much lower rates of photosensitivity with dabrafenib, but higher rates of non-specific fever. The committee concluded that an alternative BRAF-targeted treatment with a manageable adverse reaction profile, such as dabrafenib, was a potentially valuable additional treatment option for people with unresectable or metastatic melanoma.

4.2 The committee considered the clinical management of unresectable or metastatic BRAF V600 melanoma and discussed the relevant comparators for this appraisal. It was aware that in its evidence submission the company compared dabrafenib with dacarbazine and vemurafenib, and not with any other comparators specified in the scope (including temozolomide in people with brain metastases and ipilimumab in previously treated people). The committee noted the consultees' statement, confirmed by the clinical specialist, that the management of metastatic melanoma is rapidly evolving, with several ongoing clinical trials, and there is uncertainty about how these treatments would be sequenced in future. The committee heard from the clinical specialist that vemurafenib is the current standard of care for people with BRAF V600 mutation-positive melanoma because it is a targeted therapy. The committee heard from the clinical specialist

and noted the statements from consultees that ipilimumab, which is now available for first- and second-line use, is more commonly used in a subgroup of patients with good performance status and in whom the disease is not progressing rapidly. The committee also heard that dacarbazine is no longer routinely used as a first-line treatment in clinical practice and would now be used only further down the treatment pathway, probably as a third-line option. The clinical specialist also stated that temozolomide is not a standard drug used in people with brain metastases and that there was no evidence that it results in a better outcome than the targeted therapies. The committee accepted the views of the clinical specialists that in those patients being considered for dabrafenib treatment, the relevant comparator is the alternative BRAF-targeted therapy vemurafenib.

Clinical effectiveness

4.3 The committee considered the clinical effectiveness of dabrafenib and noted that the key clinical evidence in the company's submission came from the BREAK-3 trial, which compared dabrafenib with dacarbazine. It discussed the relevance of the BREAK-3 trial, given that dacarbazine is no longer considered established clinical practice in the UK. It heard from the clinical specialist that dabrafenib and vemurafenib were developed at around the same time and that dacarbazine was the standard of care when the BREAK-3 trial was conducted. It also noted the comment in the company's submission that although dacarbazine is no longer widely used in this setting, results from BREAK-3 allow an indirect comparison of dabrafenib with vemurafenib. The committee concluded that the BREAK-3 trial was relevant for this appraisal.

4.4 The committee examined the results of BREAK-3 presented by the company. It noted that dabrafenib reduces the risk of progression compared with dacarbazine, with a statistically significant difference of 4.2 months in median time to progression. The committee was aware that for overall survival, the point estimate for the hazard ratio suggested that dabrafenib results in an overall survival benefit, but that the difference did not reach statistical significance. The committee noted the high level of crossover (57%) in the trial and was aware that even after adjusting for crossover using the RPSFT method (see section 3.22) the company's estimate of overall survival gain did not reach statistical significance.

The committee was aware of the ERG's concerns about the appropriateness of the RPSFT method (see section 3.22); however, it did not think it was necessary to discuss the issue further because it considered vemurafenib to be the relevant comparator for this appraisal. The committee noted that the relatively low numbers in the dacarbazine arm of the trial (3:1 randomisation) and the high rates of crossover made it very difficult to draw a firm conclusion about the precise effect on overall survival. The committee concluded that compared with dacarbazine, dabrafenib significantly improved progression-free survival and probably improved overall survival, but it was unable to draw firm conclusions about the magnitude of overall survival benefit.

4.5 The committee went on to discuss the clinical effectiveness evidence for dabrafenib compared with vemurafenib, which is based on an indirect comparison using data from the BREAK-3 and BRIM-3 trials. The committee understood the ERG's concern that the proportional hazards assumption that this analysis relied upon was not supported by the trial data. It noted the ERG's comment that lactate dehydrogenase levels differed between BREAK-3 and BRIM-3, which suggests that patients in BRIM-3 had worse prognoses than patients in BREAK-3 (see section 3.23), and that the median overall survival in the dacarbazine arm in BREAK-3 was better than in BRIM-3 (15.6 months compared with 9.6 months).The committee heard from the clinical specialist that although lactate dehydrogenase 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. The committee noted that patients were otherwise well matched in the BREAK-3 and BRIM-3 trials, including for the stage of disease. The clinical specialist highlighted that BRIM-3 was conducted in the UK, where there may be a more conservative approach to treatment initiation than outside the UK where BREAK-3 was conducted, and that the crossover criteria differed in the 2 trials. The committee noted the statement from consultees that 'the BREAK-3 trial convincingly shows that dabrafenib is as active as vemurafenib, in terms of response rate and progression-free and overall survival hazard ratios compared with the standard arm, dacarbazine'. The committee also heard from the clinical specialist that the clinical effectiveness of dabrafenib and vemurafenib were not considered to differ in clinical practice and that the choice between the 2 treatments would be largely based on their adverse reaction profiles. The committee considered that BRIM-3 was a large trial and could show an overall survival benefit with vemurafenib, whereas BREAK-3 was a smaller trial and it

would be more difficult to demonstrate a statistically significant overall survival benefit with dabrafenib. The committee also noted that the progression-free survival gains in the 2 trials were very similar, and 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.

4.6 The committee considered the adverse reactions associated with dabrafenib. It noted that pyrexia, cutaneous squamous cell carcinoma and back pain were the most commonly reported grade-3 adverse reactions with dabrafenib. It heard from the clinical specialist that cutaneous squamous cell carcinoma was also an issue with vemurafenib. The clinical specialist stated that these targeted therapies are not given to people with serious medical conditions and are administered only in specialist centres with the ability to manage the skin malignancies that may occur. The committee heard from the clinical specialist that some clinicians may prefer dabrafenib to vemurafenib because of lower rates of photosensitivity, which may be a major problem for some patients. The clinical specialist indicated that photosensitivity could also occur with dabrafenib, but in their experience the incidence was much lower than with vemurafenib. The committee concluded that the current evidence suggests that adverse reactions from dabrafenib treatment were not a major concern when compared with those from alternative treatments and that the relative adverse reaction profile would be taken into account in discussions between patients and oncologists on the choice of the most appropriate therapy.

Cost effectiveness

4.7 The committee discussed the company's cost-effectiveness analysis. The committee had previously heard from the clinical specialist that dacarbazine was not an appropriate comparator and that people eligible for treatment with a BRAF inhibitor would not be given dacarbazine in clinical practice. Therefore it did not consider the cost effectiveness of dabrafenib compared with dacarbazine any further; it restricted its cost-effectiveness discussion to the comparison with vemurafenib.

4.8 The committee considered the company's economic model and the ERG's critique of the model. It noted the ERG's concerns regarding the structure of the model; in

particular, the way the company modelled the clinical effectiveness estimates using a 3-stage approach, resulting in survival curves that did not appear clinically plausible. The committee also noted the ERG's concerns with the company's indirect comparison (see section 3.23) and noted that the ERG had not carried out exploratory analyses of the clinical or cost effectiveness of dabrafenib compared with vemurafenib.

4.9 The committee considered whether dabrafenib was a cost-effective use of NHS resources. It noted that the company's base case ICER was £11,000 per QALY gained for dabrafenib compared with vemurafenib, but was much lower than this if a class effect was assumed for dabrafenib and vemurafenib (see section 3.20). The committee noted the ERG's comments on the limitations of the company's model but was aware that the ERG did not conduct exploratory analyses because of its concerns that any estimated ICERs generated from the results of the company's indirect comparison would be unreliable. In the absence of any further numerical analysis by the ERG, the committee could not give an estimate of the most plausible ICER for the comparison of dabrafenib with vemurafenib. However, having considered the lack of evidence of difference in clinical effectiveness between the treatments, and that the overall costs were not different in the economic analysis, the committee concluded that 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. As a result, dabrafenib should be recommended as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma.

Summary of appraisal committee's key conclusions

Key conclusion

- Section 1.1: 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.
- Section 4.4: The committee concluded that compared with dacarbazine, dabrafenib improved progression-free survival and probably improved overall survival, but it was unable to draw firm conclusions about the magnitude of overall survival benefit.

- Section 4.5: The committee concluded that it was likely that dabrafenib and vemurafenib did not differ in clinical effectiveness and that it would not be unreasonable to assume that they have similar effect.
- Sections 4.2 and 4.7: The committee concluded that vemurafenib was the most appropriate comparator, and therefore restricted its cost-effectiveness discussions to the comparison with vemurafenib.
- Section 4.9: Having considered the lack of evidence of difference in clinical effectiveness between dabrafenib and vemurafenib, and that the overall costs were not different in the economic analysis, the committee concluded that 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.

Current practice

Clinical need of patients, including the availability of alternative treatments

- Sections 4.1 and 4.2: The committee heard from the patient expert that metastatic melanoma can be associated with severe and debilitating symptoms. It heard from the clinical specialist that vemurafenib is the current standard of care for people with BRAF V600 mutation-positive melanoma because it is a targeted therapy.

The technology

How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?

- Section 4.1: The committee heard that 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, in some cases enabling them to resume everyday tasks and activities. The patient expert also stated that people may experience very few side effects with dabrafenib. The clinical specialist explained that the side-effect profile of dabrafenib differed from that of vemurafenib in that there were much lower rates of photosensitivity with dabrafenib, but higher rates of non-specific fever. The committee concluded that an alternative BRAF-targeted treatment with a manageable adverse reaction profile, such as dabrafenib, was a potentially valuable additional treatment option for people with

unresectable or metastatic melanoma.

What is the position of the treatment in the pathway of care for the condition?

- Section 4.2: The committee noted the consultees' statement, confirmed by the clinical specialist, that the management of metastatic melanoma is rapidly evolving, with several ongoing clinical trials, and there is uncertainty about how these treatments would be sequenced in future. The committee accepted the views of the clinical specialists that in those patients being considered for dabrafenib treatment, the relevant comparator is the alternative BRAF targeted therapy vemurafenib.

Adverse reactions

- Section 4.6: The committee concluded that the current evidence suggests that adverse reactions from dabrafenib treatment were not a major concern when compared with those from alternative treatments and that the relative adverse reaction profile would be taken into account in discussions between patients and oncologists on the choice of the most appropriate therapy.

Evidence for clinical effectiveness

Availability, nature and quality of evidence

- Section 4.3: The committee noted that the key clinical evidence in the company's submission came from the BREAK-3 trial, which compared dabrafenib with dacarbazine.
- Section 4.5: The committee discussed the clinical effectiveness evidence for dabrafenib compared with vemurafenib; which is based on an indirect comparison using data from the BREAK-3 and BRIM-3 trials.

Relevance to general clinical practice in the NHS

- Section 4.3: The committee noted that dacarbazine was the standard of care when the BREAK-3 trial was conducted and that the results of the BREAK-3 trial allow an indirect comparison of dabrafenib with vemurafenib. The committee concluded that the BREAK-3 trial was relevant for this appraisal.

Uncertainties generated by the evidence

- Sections 4.4 and 4.5: The committee noted the high level of crossover in the BREAK-3 trial and was aware that even after adjusting for crossover using the rank preserving structural failure time (RPSFT) method, the company's estimate of overall survival gain did not reach statistical significance. The committee understood the ERG's concern that the proportional hazards assumption that the indirect comparison relied upon was not supported by the trial data.

Estimate of the size of the clinical effectiveness including strength of supporting evidence

- Sections 4.4 and 4.5: The committee concluded that, compared with dacarbazine, dabrafenib significantly improved progression-free survival by 4.2 months and probably improved overall survival, but it was unable to draw firm conclusions about the magnitude of overall survival benefit. In light of the available evidence, the committee concluded that it was likely that dabrafenib and vemurafenib did not differ in clinical effectiveness and that it would not be unreasonable to assume that they have similar effect.

Evidence for cost effectiveness

Availability and nature of evidence

- Section 4.7: The committee did not consider the cost effectiveness of dabrafenib compared with dacarbazine, having noted that dacarbazine was not an appropriate comparator as it was no longer used in clinical practice. It restricted its cost-effectiveness discussion to the comparison with vemurafenib.

Uncertainties around and plausibility of assumptions and inputs in the economic model

- Section 4.8: The committee noted the ERG's concerns regarding the structure of the model; in particular, the way the company modelled the clinical effectiveness estimates using a 3-stage approach, resulting in survival curves that did not appear clinically plausible. The committee also noted the ERG's concerns with the company's indirect comparison and noted that the ERG had not carried out exploratory analyses

of the clinical or cost effectiveness of dabrafenib compared with vemurafenib.

Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

- Section 3.16: Treatment-specific EQ-5D utility data for pre-progression and post-progression, derived directly from BREAK-3, were used in the model for dabrafenib and dacarbazine. In the absence of comparable EQ-5D utility data for vemurafenib, the company assumed that the vemurafenib utility values would be the same as those for dabrafenib.

What are the key drivers of cost effectiveness?

- Section 3.20: The company conducted a series of deterministic sensitivity analyses. For the comparison of dabrafenib with dacarbazine, overall survival was the key driver of the cost-effectiveness results. The key driver of the cost-effectiveness result for the comparison of dabrafenib with vemurafenib was the progression-free survival assumption.

Most likely cost-effectiveness estimate (given as an ICER)

- Section 4.9: The committee noted that the company's base case ICER was £11,000 per QALY gained for dabrafenib compared with vemurafenib, but was much lower than this if a class effect was assumed for dabrafenib and vemurafenib. In the absence of any further numerical analysis by the ERG, the committee could not give an estimate of the most plausible ICER for the comparison of dabrafenib with vemurafenib.

Additional factors taken into account

Patient access schemes (PPRS)

- Section 2.3: Novartis has agreed a patient access scheme with the Department of Health that makes dabrafenib available with a discount applied at the point of purchase or invoice. The size of the discount is commercial in confidence.

Equalities considerations and social value judgements

- No equality issues relevant to the committee's recommendations were raised.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has unresectable or metastatic BRAF V600 mutation-positive melanoma and the doctor responsible for their care thinks that dabrafenib is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and the company have agreed that dabrafenib will be available to the NHS with a patient access scheme that makes dabrafenib available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the Novartis Commercial Operations team on 01276 698717 or commercial.team@novartis.com.

6 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The appraisal committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. There are 4 appraisal committees, each with a chair and vice chair. Each appraisal committee meets once a month, except in December when there are no meetings. Each committee considers its own list of technologies, and ongoing topics are not moved between committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Professor Thanos Athanasiou
Professor of Cardiovascular Sciences and Cardiac Surgery, Imperial College London; Consultant Cardiothoracic Surgeon, Imperial College Healthcare NHS Trust

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Gerardine Bryant
GP, Swadlincote, Derbyshire

Dr Simon Bond
Senior Statistician, Cambridge Clinical Trials Unit

Dr Andrew England
Senior Lecturer, Directorate of Radiography, University of Salford

Mr Adrian Griffin
Vice President, HTA & International Policy, Johnson & Johnson

Dr Peter Heywood
Consultant Neurologist, Frenchay Hospital, Bristol

Dr Sharon Saint Lamont
Head of Clinical Quality, NHS England (North)

Dr Louise Longworth
Reader in Health Economics, HERG, Brunel University

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray
Professor of Medical Cardiology, University of Glasgow

Dr Mohit Misra
GP, Queen Elizabeth Hospital, London

Mrs Sarah Parry
CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Mrs Pamela Rees
Lay Member

Dr Ann Richardson
Lay Member

Mr Stephen Sharp
Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Peter Sims
GP, Devon

Mr David Thomson
Lay Member

Professor Olivia Wu
Professor of Health Technology Assessment, University of Glasgow

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker
Technical Lead

Nwamaka Umeweni
Technical Adviser

Bijal Joshi
Project Manager

7 Sources of evidence considered by the committee

The evidence review group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):

- Fleeman N, Bagust A, Beale S (2014) Dabrafenib for treating unresectable, advanced or metastatic BRAF V600 mutation-positive melanoma: A single technology appraisal.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). The company/sponsor was also invited to make written submissions. Professional/specialist and patient/carer groups and other consultees had the opportunity to give their expert views and, along with the company/sponsor, also have the opportunity to appeal against the final appraisal determination.

- Company/sponsor:
  - GlaxoSmithKline
- Professional/specialist and patient/carer groups:
  - British Association of Dermatologists
  - British Association of Skin Cancer Specialist Nurses
  - British Dermatological Nursing Group
  - Cancer Research UK
  - Melanoma Focus
  - Melanoma UK
  - Royal College of Nursing
  - Royal College of Pathologists
  - Royal College of Physicians

- Other consultees:
  - Department of Health
  - NHS England
- Commentator organisations (did not provide written evidence and without the right of appeal):
  - Bristol-Myers Squibb
  - Department of Health, Social Services and Public Safety for Northern Ireland
  - Healthcare Improvement Scotland
  - Institute of Cancer Research
  - Liverpool Reviews & Implementation Group, University of Liverpool
  - MRC Clinical Trials Unit
  - National Collaborating Centre for Cancer
  - National Institute for Health Research Health Technology Assessment Programme
  - Roche Products

The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on dabrafenib by attending the initial committee discussion and providing written evidence to the committee.

- Dr Pippa Corrie, Consultant and Associate Lecturer in Medical Oncology, nominated by NCRI/RCP/RCR/ACP/JCCO – clinical specialist
- Gillian Nuttall, Chief Executive Officer, nominated by Melanoma UK – patient expert
- Sarah Garner, Patient carer, nominated by Melanoma UK – patient expert.

Representatives from the following company/sponsor attended committee meetings. They contributed only when asked by the committee chair to clarify specific issues and comment on factual accuracy.

- GlaxoSmithKline.

Update information

Minor changes since publication

April 2017: The company changed from GlaxoSmithKline to Novartis. Contact details for the patient access scheme were updated.

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Accreditation