NICE National Institute for Health and Care Excellence

NICE guidance

Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant 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.

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1 Recommendations

1.1 Vemurafenib is recommended as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme.

2 The technology

2.1 Vemurafenib (Zelboraf, Roche Products) is an oral tyrosine kinase inhibitor of the oncogenic BRAF V600 protein kinase. It has a UK marketing authorisation for 'the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma'. All people starting treatment with vemurafenib should have a positive test for the BRAF V600 mutation. Vemurafenib was developed alongside the Roche cobas 4800 BRAF V600 mutation test, which is commercially available in the European Union.

2.2 Vemurafenib is most commonly associated with the following adverse reactions: arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus. It can also lead to the formation of cutaneous squamous-cell carcinomas. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The recommended dose of vemurafenib is 960 mg (4×240 mg tablets) twice daily (equivalent to a total daily dose of 1,920 mg). The summary of product characteristics states that the doses should be given approximately 12 hours apart, and that treatment with vemurafenib should continue until 'disease progression or the development of unacceptable toxicity'. Vemurafenib costs £1,750 for 1 pack of 56×240 mg tablets (1 week's supply; excluding VAT; BNF September 2012). Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of vemurafenib has agreed a patient access scheme with the Department of Health, in which a discount on the list price of vemurafenib is offered. 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 manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of vemurafenib and a review of this submission by the Evidence Review Group (ERG). The decision problem addressed by the manufacturer considered people with BRAF V600 mutation-positive melanoma who have not previously received treatment, which is in contrast to the original decision problem that allowed for vemurafenib to be considered in both first- and subsequent-line treatment settings.

3.1 The key clinical evidence came from 1 multicentre, randomised, open-label, active-controlled trial (BRIM3) that compared vemurafenib (960 mg twice daily orally; n=337) with dacarbazine (1,000 mg per square metre of body surface area by intravenous infusion every 3 weeks; n=338) in adults with previously untreated stage 3c or 4 BRAF V600 mutation-positive metastatic melanoma, until disease progression or unacceptable toxicity. The randomisation process produced equivalent-sized groups. However, 14% of patients (48 of 338) randomised to receive dacarbazine did not receive treatment, primarily because they withdrew consent or refused treatment. The median age of patients in the trial was 56 years for people receiving vemurafenib and 52 years for those receiving dacarbazine. About 60% of patients were from western Europe, and the proportion of patients with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 was 68% in both the vemurafenib and dacarbazine groups. At study entry, more than 90% of patients had stage 4 disease.

3.2 The primary outcome in the BRIM3 study changed from overall survival to a joint primary outcome of overall survival and progression-free survival during the study, at the request of the US Food and Drug Administration. Secondary outcomes included confirmed best overall response rate, duration of response and time to response.

3.3 The manufacturer presented 3 analyses for overall survival based on 3 different data cut-off points (December 2010, March 2011 and October 2011). The Data and Safety Monitoring Board recommended the release of the interim results of efficacy, based on a review of the results of the planned interim analysis of overall survival, and the study was ended and crossover allowed at this time (December 2010). The manufacturer performed 2 additional analyses (using

March 2011 and October 2011 data cut-off time periods) to demonstrate the survival benefit conferred by vemurafenib during follow-up.

3.4 Results from the December 2010 data cut-off of the BRIM3 trial showed that treatment with vemurafenib led to a statistically significant reduction in death (hazard ratio [HR] 0.37; 95% confidence interval [CI] 0.26 to 0.55; p<0.001). At 6 months, overall survival was 84% (95% CI 78 to 89) in the vemurafenib group and 64% (95% CI 56 to 73) in the dacarbazine group. People treated with vemurafenib also had a statistically significant reduction in tumour progression (HR 0.26; 95% CI 0.20 to 0.33; p<0.001). The estimated median progression-free survival (evaluated in 549 patients) was 5.32 months (95% CI 4.86 to 6.57) in the vemurafenib group and 1.61 months (95% CI 1.58 to 1.74) in the dacarbazine group.

3.5 The secondary outcome of confirmed tumour response could be calculated for 439 patients for the December 2010 data cut-off. In the vemurafenib treatment group, 106 of 219 patients (48%; 95% CI 42 to 55) had a confirmed objective response (including 2 patients with a complete response and 104 patients with a partial response), with a median time to response of 1.45 months. Only 12 of the 220 patients (5%; 95% CI 3 to 9) treated with dacarbazine had a partial response (no patients had a complete response), with a median time to response of 2.7 months.

3.6 Results from the March 2011 data cut-off included 50 patients (15%) who switched from dacarbazine to vemurafenib. The censored hazard ratio for overall survival was 0.44 (95% CI 0.33 to 0.59). Results from the October 2011 data cut-off, which included 24% (n=81) of patients who switched from dacarbazine to vemurafenib on disease progression, showed that median overall survival was 13.2 months for the vemurafenib group and 9.6 months for people treated with dacarbazine (censored HR 0.62; 95% CI 0.49 to 0.77).

3.7 In response to consultation, the manufacturer also presented results based on the February 2012 data cut-off. This included data on 34% of patients who switched over from dacarbazine to vemurafenib and other BRAF inhibitors. Results showed that treatment with vemurafenib led to a statistically significant progression-free survival benefit (HR 0.38; 95% CI 0.32 to 0.46; p<0.001) compared with dacarbazine. Median overall survival was 13.6 months in the

vemurafenib group and 10.3 months in the dacarbazine group (uncensored HR 0.76; 95% CI 0.63 to 0.93; p<0.01). Tumour response rate (defined as at least a 30% reduction in tumour size) was 57% (192 out of 337 patients) in the vemurafenib group compared with 8.6% in the dacarbazine group. In the vemurafenib group, 5.6% of patients had a complete response (that is, the disappearance of all disease), compared with 1.2% in the dacarbazine arm.

3.8 The manufacturer reported results from a range of pre-specified subgroups, including age, sex, ECOG performance status, tumour stage and geographical regions. The results showed that the survival benefit conferred by vemurafenib treatment was generally maintained across each subgroup.

3.9 The most commonly reported adverse events (grade 2 or more) associated with vemurafenib treatment in the BRIM3 study were cutaneous events, arthralgia and fatigue (December 2010 cut-off based on 618 patients). People treated with dacarbazine experienced fatigue, nausea, vomiting and neutropenia. A total of 61 people (18%) treated with vemurafenib experienced grade 3 cutaneous squamous-cell carcinoma, keratocanthoma or both, and were treated with simple excision. Treatment-related adverse events were recorded for more people who received vemurafenib, which may be explained by the fact that they stayed on treatment longer than those who received dacarbazine (3.1 months for vemurafenib compared with 0.76 months for dacarbazine based on the December 2010 data cut-off). Adverse events led to dose modification or treatment interruption in 38% of patients in the vemurafenib group (129 of 336 patients) and in 16% of patients receiving dacarbazine (44 of 282 patients). The most common reasons for dose modification were an adverse event or missed cycle. There were more adverse events that led to discontinuation in patients treated with vemurafenib than with dacarbazine (88 compared with 15 patients).

3.10 The manufacturer undertook a systematic literature search but did not identify any economic evaluations of vemurafenib for previously untreated patients with advanced BRAF V600 mutation-positive metastatic malignant melanoma. Therefore, the manufacturer submitted a de novo 'partitioned survival' economic model in which vemurafenib was compared with dacarbazine. The model comprised 3 health states: progression-free, progressed disease and death. Hypothetical patients were assumed to enter the model in the progression-free

health state and either remain in that state or progress to a worse health state (that is, progressed disease or death) at the end of each cycle. The model used weekly cycles for a lifetime (30-year) horizon. The perspective adopted in the economic evaluation was that of the NHS and personal social services, and costs and benefits were discounted at 3.5% per year.

3.11 The proportion of people in each health state in the manufacturer's original model was calculated using progression-free survival and overall survival data (March 2011 data cut-off) from the BRIM3 study. The probability of remaining in the progression-free state was calculated using results observed in the BRIM3 study until month 9 for vemurafenib and month 7 for dacarbazine, after which progression-free survival for each intervention was extrapolated using exponential functions. Overall survival for patients treated with vemurafenib was estimated directly from the BRIM3 study for the first 9.5 months (March 2011 data cut-off). A 'stabilised' hazard ratio representing the differences between the vemurafenib and dacarbazine arms up to month 14 was then applied, after which the manufacturer assumed that vemurafenib provided no further treatment benefit (that is, a hazard ratio of 1 was assumed). The estimate of overall survival in the dacarbazine arm was based on 3 different sets of data. The cumulative hazard of overall survival in the BRIM3 study was used directly for 40 weeks (9.2 months), with the longer-term outcomes up to 46 months derived from a study by Robert et al. (2011), which compared ipilimumab plus dacarbazine with dacarbazine alone in people with previously untreated advanced melanoma. For months 46 and beyond, a long-term hazard estimate taken from the Surveillance, Epidemiology and End Results (SEER) register was used.

3.12 The manufacturer collected health-related quality-of-life data in the BRIM3 study using the functional assessment of cancer therapy melanoma (FACT-M) questionnaire; however, results were not presented because completion rates were low. Instead, utility values from a study by Beusterien et al. (2009) were used. In this study, standard gamble methods were used to elicit utilities for advanced melanoma health states from members of the general public. These were combined with disutility values associated with adverse events (obtained from Beusterien et al. [2009] and another study by Nafees et al. [2008]). In the manufacturer's base case analysis, a utility for progression-free survival of 0.806 was calculated for people receiving vemurafenib and 0.767 for people receiving dacarbazine. The utility for progressed disease was estimated to be 0.59 based

on the study by Beusterien et al. (2009).

3.13 Adverse event rates for vemurafenib and dacarbazine were estimated from the BRIM3 study. The resource costs included in the model were drug acquisition and administration costs, the cost of testing for the BRAF V600 mutation, and the cost of the disease, which included costs related to each health state and of treating adverse events. The average length of a course of treatment with vemurafenib was assumed to be 7 months.

3.14 In the manufacturer's original base-case analysis (using the March 2011 data cut-off), the incremental cost-effectiveness ratio (ICER) for vemurafenib compared with dacarbazine was £56,410 per quality-adjusted life year (QALY) gained (incremental costs and benefits provided as commercial in confidence; patient access scheme included). When the October 2011 data cut-off point was used instead, the ICER increased to £75,489 per QALY gained.

3.15 The manufacturer undertook a series of sensitivity analyses to test the robustness of the results by varying most of the parameters used in the original economic evaluation, including transition probabilities, utilities, costs, discount rate, average age of patients, and BRAF V600 mutation incidence. Taking into account the patient access scheme, the ICERs indicated that vemurafenib was most sensitive to the discount rate (for example, when health benefits were discounted at 1.5% and 0%, the base-case ICER decreased to £48,249 and £42,054 per QALY gained respectively) and variations to the assumed hazard of death between months 9 and 14. The manufacturer also provided additional scenario analyses that modelled the impact on the ICER of using different utility estimates from Hodi et al. 2010 (which compared ipilimumab plus gp100 with gp100 alone and with ipilimumab alone). When utility values were selected from this study for progression-free survival (0.80) and progressed disease (0.76) and applied to vemurafenib and dacarbazine in the base case, the ICER fell to £50,052 per QALY gained.

3.16 The ERG considered the BRIM3 study to be well designed and that the clinical-effectiveness evidence presented by the manufacturer was relevant to the decision problem. The ERG noted that the data from the BRIM3 study demonstrated a statistically significant difference for both overall survival and progression-free survival for vemurafenib over dacarbazine in patients who had

not received previous treatment. It cautioned, however, that the short-term nature of the results from the BRIM3 study and the heterogeneity of the patient population led to substantial uncertainty when projecting long-term benefits of treatment.

3.17 The ERG questioned some of the manufacturer's assumptions relating to the costs in the original model, and provided some alternative cost estimates. These included a re-estimation of costs for dacarbazine therapy based on distributions of body weight and body surface area found in a cohort of UK patients, and the assumption that dacarbazine would be administered as an oncology day case. The ERG also queried long-term monitoring costs (that is, computed tomography [CT] scan and outpatient visits to an oncologist) for both vemurafenib and dacarbazine with clinical advisers, and found that a programme of 3 to 4 times per year for 2 years, then twice a year for 2 years, and then finally once a year thereafter was more likely than the manufacturer's estimate.

3.18 The ERG acknowledged that the manufacturer adapted an economic model previously used in NICE technology appraisals of cancer drugs in its original submission. It expressed concern that the manufacturer's approach to modelling overall survival was overly elaborate and disagreed with the following methods in the manufacturer's original model:

- Survival gains over dacarbazine continued to accrue after vemurafenib treatment was stopped (that is, the vemurafenib group continued to have a lower risk of death) through the application of a hazard ratio estimated from the BRIM3 data to extend the treatment benefit of vemurafenib to 14 months.
- The use of a small sample of an arm of the Robert et al. (2011) trial to provide estimates for modelling the outcomes of patients receiving dacarbazine and of those receiving vemurafenib beyond 14 months of survival to 46 months.
- Representing the long-term survival beyond 46 months by a single mortality risk factor parameter calibrated to reconcile data from the study by Robert et al. (2011) with a single value from the SEER database at 10 years (ignoring the SEER hazard profile of more than 1,000 patients).

3.19 The ERG explored an alternative approach to modelling overall survival. After examining the Kaplan–Meier overall survival curves from the BRIM3 study, the

ERG proposed that vemurafenib is effective at suppressing disease progression leading to death in the early phase (on average 97 days) but, after a short period, this effect stops and patients revert to the pattern of mortality risk seen in the dacarbazine arm. The ERG suggested that the assumption of a limited window of effectiveness might be supported by the observation that resistance is common with tyrosine kinase inhibitor drugs, reflecting the fact that cancer cells use multiple signalling pathways. The ERG further suggested that there appear to be 2 distinct populations of patients with malignant melanoma: the majority who have a poor prognosis and have a high risk of death within 12 months; and a small group who appear to have good prognosis and can survive for 10 years or more. To address this, the ERG used a simple survival model that included each subgroup split in an unknown ratio and governed by a separate long-term mortality risk (equivalent to an exponential function). The ERG used a study by Balch et al. (2009) to construct a case-mix-adjusted survival curve. This study provided survival curves for each of 4 metastatic melanoma categories (M0: no distant metastases; M1a: distant skin, subcutaneous, or nodal metastases; M1b: metastases to lung; M1c: metastases to all other visceral sites or distant metastases to any site combined with an elevated serum lactate dehydrogenase) based on the American Joint Committee on Cancer Melanoma Staging Database. The ERG constructed the survival curve according to the proportions of patients in the BRIM3 study with each melanoma category (15.9% melanoma stage M0/ M1a, 18.8% M1b and 65.3% M1c). The ERG then fitted a 2-part exponential model to take into account its view of 2 distinct melanoma populations (as described above). The ERG's compound survival model and the BRIM3 case-mix-adjusted survival curve showed strong similarities, with the compound survival model indicating that 80.6% of patients would have a mean survival of 11 months (0.91 years) and 19.4% of people with advanced melanoma would have an expected mean survival of more than 12 years (145 months).

3.20 After consultation on preliminary guidance, the manufacturer submitted revised cost-effectiveness estimates, which incorporated updated survival evidence from the February 2012 data cut-off of the BRIM3 study. The revised survival estimates were adjusted for patients who switched from dacarbazine to vemurafenib on disease progression (using the rank preserving structural failure time [RPSFT] method). The manufacturer justified using the RPSFT method because it has been previously accepted in a number of NICE technology appraisals. It noted that the RPSFT method did not take into account patients

who switched to other BRAF inhibitors (not including vemurafenib) or investigational compounds. Using the RPSFT method, the manufacturer's adjusted estimate of median overall survival in the dacarbazine arm decreased from 10.3 months to 8.9 months (HR 0.64; 5% CI 0.53 to 0.78; p<0.0001). After incorporating the adjusted survival hazard ratio into the model and taking into account the ERG's suggested amendments to discounting, costs and utility for long-term survivors (see sections 3.15 and 3.17) the manufacturer's revised base-case ICER was £52,327 per QALY gained.

3.21 After a request from the Committee, the manufacturer provided a full explanation of the assumptions made and parameters used for the RPSFT method, which adjusted the survival estimates for patients who switched from dacarbazine to vemurafenib at disease progression. The manufacturer noted that the RPSFT method attempts to simulate a control arm of people who have not crossed over from dacarbazine to vemurafenib by applying an acceleration factor that 'speeds up' the time for people receiving vemurafenib after disease progression. The manufacturer noted the following key assumptions underlying the RPSFT method:

- There is a single underlying acceleration factor associated with the intervention that does not vary with time. The RPSFT method defines an 'average' acceleration factor across all the patients who received the intervention and then applies this to those patients who switched treatments only.
- The acceleration factor is valid for patients randomised to the vemurafenib group, and those in the group who switch from dacarbazine to vemurafenib, and also that the treatment is equally effective as a second-line and as a first-line treatment.

3.22 The manufacturer stated that the first assumption (the acceleration factor does not vary with time) does not hold for the BRIM3 data. Data from the BRIM3 study suggest that the effect of vemurafenib on mortality is highest within the first few months of treatment and the average acceleration factor of 0.34 estimated from the BRIM3 study was likely to under-accelerate the survival times of patients who switched from dacarbazine to vemurafenib on disease progression. The manufacturer considered that this would result in a lower calculated survival benefit for vemurafenib than the true benefit. The manufacturer also discussed the plausibility of using alternative approaches to adjust for switching (namely,

censoring patients at the point of crossover, inverse probability censoring weighting and the Branson and Whitehead method), but found these methods to be inappropriate in light of the BRIM3 trial data.

3.23 After a request from the Committee, the manufacturer provided a discussion on the use of data from other trials in which no crossover occurred to represent the clinical effectiveness of dacarbazine. The manufacturer compared patient populations in the BRIM3 trial to populations in other trials that included dacarbazine as a comparator. It found some similarity across trials but noted inconsistent reporting of known prognostic factors such as the proportion of patients with elevated lactate dehydrogenase. One trial, Bedikian et al. (2011), evaluated dacarbazine in a malignant melanoma population and had similar patient characteristics in terms of age and stage of disease as the BRIM3 trial. The manufacturer expressed caution about using external data from other trials to model survival in the dacarbazine arm but included an analysis using the Bedikian trial as a sensitivity analysis in its submission (see section 3.25).

3.24 The Committee asked the manufacturer to provide an additional scenario analysis that compared vemurafenib with dacarbazine, in which exponential hazards were applied separately to each arm of the BRIM3 study (using February 2012 data cut-off) from 14 months onward. The manufacturer declined to provide this scenario analysis. It said that this extrapolation gave a post-progression survival after treatment with vemurafenib that was 2.2 months shorter than post-progression survival after dacarbazine, which it considered implausible. It considered that this implausible result may be because of an under-adjustment of the acceleration factor used in the RPSFT method, and cautioned against using this extrapolation. The manufacturer further justified its decision not to provide the additional scenario analysis on the basis that register data shows that probability of death associated with melanoma reduces over time and an exponential model assumes a constant probability over time. As a result, any calculation based on exponential modelling will have poor external validity.

3.25 The manufacturer provided revised cost-effectiveness estimates for vemurafenib compared with dacarbazine of £51,757 per QALY gained (using the RPSFT-adjusted February 2012 data and incorporating the ERG's suggested adjustments), and £44,405 using the Bedikian trial data to represent the dacarbazine arm (including the ERG's adjustments).

3.26 The ERG commented on the manufacturer's additional information about the impact of switching treatment from dacarbazine to vemurafenib after disease progression and responded to the additional scenario analysis. The ERG disagreed with the manufacturer that a 2.2-month shorter post-progression survival with vemurafenib than dacarbazine was implausible. It commented that vemurafenib may provide only a temporary inhibition to the normal process of disease progression and that overall survival was a more objective outcome than progression-free survival. It agreed with the manufacturer that the assumption about time invariance was not met in the RPSFT method (that is, BRIM3 shows the treatment effect of vemurafenib changes over time), but disagreed that this would lead to implausible estimates for the scenario analysis that the Committee had requested. The ERG carried out the scenario analysis and reported an ICER of £120,933 per QALY gained.

Details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of vemurafenib, having considered evidence on the nature of locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma and the value placed on the benefits of vemurafenib 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 discussed the place of vemurafenib in the clinical pathway of care for people with locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. It heard from the clinical specialists that dacarbazine has been used for the past 30 years for first-line management and, although well tolerated, it needs to be administered intravenously in hospital, and is regarded as not being very effective. The Committee noted the very limited effective treatment options currently available for people with metastatic melanoma but acknowledged that there are increasing numbers of clinical trials investigating a range of new therapies for this disease. The Committee heard from the clinical specialists that vemurafenib has a high disease response rate compared with dacarbazine, and that symptomatic improvement is often rapid, even for those with very advanced disease and the accumulating clinical experience with vemurafenib is demonstrating unique clinical benefits for patients. The patient experts said that vemurafenib improves people's quality of life by alleviating symptoms within days or weeks, that it has more manageable side effects, and is easier and more convenient to use than dacarbazine because of its oral formulation. As a result, vemurafenib offers some people the opportunity to return to work and resume a normal life. The Committee heard from the clinical specialists, and accepted, that vemurafenib is a step change in the management of advanced malignant melanoma and that there is a significant need for effective therapies in this patient population.

Clinical effectiveness

4.2 The Committee considered the results presented by the manufacturer on the clinical effectiveness of vemurafenib. It noted that the manufacturer derived

efficacy data primarily from the BRIM3 trial. This showed that treatment with vemurafenib led to a statistically significant increase in median progression-free survival of 5.3 months (HR 0.38; 95% CI 0.32 to 0.46), and an increase in median overall survival of approximately 3.3 months (uncensored HR 0.76; 95% CI 0.63 to 0.93) based on the February 2012 data cut-off, compared with dacarbazine for people with previously untreated advanced or metastatic disease. The Committee also took particular note of the increase in response rate to treatment with vemurafenib over time and acknowledged the number of people whose disease responded completely to treatment with vemurafenib was 5.6% at the February 2012 data cut-off compared with 0.9% in December 2010. The Committee accepted that there could be a long-term benefit for some people and concluded that vemurafenib is a highly effective treatment for locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma.

4.3 The Committee discussed whether the BRIM3 study is generalisable to UK clinical practice. The Committee noted that patients with an ECOG performance status of 0 or 1 were included in the BRIM3 study, and discussed whether people with an ECOG performance status of 2 or 3 are likely to receive vemurafenib treatment in UK clinical practice. The Committee heard from the clinical specialists that the use of vemurafenib is unlikely to be restricted to people with a good performance status, because case studies have demonstrated that even people with the poorest prognosis can still benefit from treatment. The Committee concluded that the results of the BRIM3 study were generalisable to UK clinical practice.

4.4 The Committee considered the 4 different data cut-off points from the BRIM3 study presented by the manufacturer. It acknowledged that the Data and Safety Monitoring Board ended the study early and allowed patients to switch from dacarbazine to vemurafenib (or another treatment) on disease progression based on the evidence for the efficacy of vemurafenib after an interim analysis in December 2010. The Committee noted that vemurafenib, irrespective of the data cut-off, was superior to dacarbazine with respect to the primary endpoints of progression-free survival and overall survival, and that this was statistically significant at all data-cut-offs. The Committee acknowledged that the March 2011 cut-off data included 15% of participants who switched from dacarbazine to vemurafenib on disease progression, and that although the October 2011 and February 2012 data cut-offs provided an additional 7 months

and 11 months of data respectively, they also included a greater proportion of patients who switched from dacarbazine to vemurafenib (bringing the switching rate to 24% in October 2011 and 34% in February 2012). The Committee was cautioned by the clinical specialists and the manufacturer that the data on overall survival from the later data cut-offs were confounded not only by switching from dacarbazine to vemurafenib, but also by the fact that patients whose disease did not show an objective response were able to receive a range of other therapies including ipilimumab (another treatment for metastatic melanoma) and other investigational BRAF inhibitor treatments. The Committee acknowledged the clinical specialists' concerns but were minded to accept that more information on the long-term clinical effectiveness of vemurafenib at the February 2012 data cut-off outweighed concerns about the robustness of the data compared with the earlier data cut-offs. However, the Committee also acknowledged that in the situation in which significant numbers of trial participants switched from a drug with limited efficacy to one with much higher efficacy, it would be reasonable to consider the effect that this would have on the results in the uncensored trial arms.

4.5 The Committee discussed the issue of switching in the BRIM3 trial. It was aware that people from the dacarbazine arm could receive treatment with vemurafenib on disease progression, and recognised that this change to a more effective treatment could have confounded the calculation of overall survival benefit from vemurafenib. The Committee agreed that it was appropriate to adjust the overall survival results from the February 2012 data cut-off (which gave a median overall survival estimate of 13.6 months for vemurafenib and 10.3 months for dacarbazine, HR 0.76 [95% CI 0.63 to 0.93]) to control for switching using statistical modelling or other techniques. However, the Committee agreed that any estimate of overall survival obtained using these techniques would be subject to uncertainty.

4.6 The Committee discussed the manufacturer's approach to adjusting the survival estimate for the dacarbazine arm of the BRIM3 study (February 2012 data cut-off) to account for people who switched to vemurafenib on disease progression using the RPSFT method. The Committee considered the key assumptions outlined by the manufacturer that underpin the RPSFT method and their validity in relation to the BRIM3 study. The Committee noted that both the manufacturer and the ERG agreed that the effect of vemurafenib treatment on

mortality changes over time (see section 3.22) and that applying a single acceleration factor may therefore be an oversimplification, and that the results should be viewed with caution. To evaluate the plausibility of the ICER obtained using the RPSFT method, the Committee noted that the hazard ratio for overall survival (using February 2012 data and RPSFT adjustment) was 0.64 (95% CI 0.53 to 0.78; p<0.0001) and acknowledged that this was in line with the overall survival hazard ratio using the October 2011 data cut-off (censored HR 0.62; 95% CI 0.49 to 0.77). The Committee then considered the scenario in which external data (Bedikian et al. [2011]) were used to represent the clinical effectiveness of dacarbazine, and acknowledged similarities to the BRIM3 trial population. It expressed caution about using an external trial over data available in the BRIM3 trial, but accepted that this gave an ICER similar to, but lower than the RPSFT method, providing reassurance that the RPSFT method was a reasonable approach in this case. The Committee accepted that there was evidence that vemurafenib increased overall survival compared with dacarbazine and concluded that, of the various methods to adjust the BRIM3 trial data for crossover, the RPSFT method was the most plausible because it gave results in line with those obtained using an alternative indirect method (Bedikian et al. [2011]) for removing the effect of crossover.

4.7 The Committee discussed whether the benefit from vemurafenib over dacarbazine was likely to continue once treatment was stopped, or conversely whether there may be accelerated disease progression. It noted the concerns of the ERG that people may experience accelerated disease progression once treatment with vemurafenib is stopped. The Committee heard from the clinical specialists that people whose disease progresses after treatment with vemurafenib may have a smaller tumour burden compared with those treated with dacarbazine because of the higher disease response rate seen with vemurafenib. Therefore, on disease progression they may have a survival advantage. The clinical specialists also explained that some people will continue to experience a benefit after treatment is stopped because they have discordant progression (if only 1 area of their tumour, which can be potentially resected or treated separately, has progressed but other parts have not). The Committee acknowledged that the existence or magnitude of continued benefit from vemurafenib after treatment is stopped is uncertain, but recognised there is no evidence currently available to suggest that people who stop vemurafenib treatment will experience accelerated disease progression compared with those

who have been treated with dacarbazine.

4.8 The Committee considered the adverse events associated with treatment with vemurafenib. It noted that cutaneous events were commonly reported in the BRIM3 study, with 61 people (18%) needing treatment for grade 3 cutaneous squamous-cell carcinoma, keratocanthoma or both. The Committee heard from the clinical specialists and patient experts that people being treated with vemurafenib can have significant skin toxicities, but these are manageable with dose reductions, topical treatments or local excision of lesions. The Committee concluded that treatment with vemurafenib had an acceptable adverse event profile when taking into account the potential benefits.

Cost effectiveness

4.9 The Committee discussed the assumptions underpinning the estimate of overall survival in the manufacturer's revised economic model. It noted that the hazard ratio estimates from the February 2012 data cut-off for up to 14 months were used, and no further beneficial effect of vemurafenib on the risk of death compared with dacarbazine was assumed after 14 months (hazard ratio of 1). The Committee heard from the manufacturer that it considered its approach to modelling survival beyond 14 months to be conservative because the RPSFT method does not take into account post-progression use of ipilimumab or BRAF inhibitors other than vemurafenib, which both favour the dacarbazine arm. The clinical specialists stated that treatment with vemurafenib could alter the biology of the disease and could potentially have a beneficial impact on the post-progression survival of patients. They also stated that there was no trial evidence or clinical evidence that patients who progressed after vemurafenib treatment did so any faster than those who had received dacarbazine as was suggested both in the ERG's original exploratory approach, and in the scenario analysis requested by the Committee. The Committee therefore accepted the manufacturer's assumption that patients in both treatment arms would have an equal risk of death beyond 14 months. The Committee also noted that the ERG, and to a lesser extent the manufacturer, relied on register data to predict long-term survival in the dacarbazine arm. These data are historical, may be subject to selection or treatment centre bias, and are pooled data that are not specific for BRAF-positive patients. The Committee considered that this further contributed to the

uncertainty about the most robust approach to modelling long-term survival, but found no evidence that accelerated disease progression occurred in vemurafenib-treated patients compared with those treated with dacarbazine beyond 14 months.

4.10 The Committee discussed the ERG's exploration of an alternative approach to modelling overall survival. It noted that the ERG used the October 2011 data cut-off and assumed that, after 14 months, the benefit of vemurafenib decreased, and the rate of death exceeded that in the dacarbazine arm until the 2 survival arms converged by 4 years, after which, the risk of death in the vemurafenib and dacarbazine arms would be equal. This resulted in a calculated mean overall survival benefit of 97 days for patients treated with vemurafenib compared with those who received dacarbazine, which the Committee noted was less than the median overall survival benefit of 3.6 months demonstrated in the October 2011 data cut-off in the trial. The Committee reiterated its conclusion that there was significant uncertainty about the magnitude of the survival benefit attributable to vemurafenib but concluded that there was no evidence to support disease acceleration after vemurafenib treatment relative to dacarbazine, as occurred in the ERG's exploratory analysis. The Committee therefore accepted the manufacturer's approach to modelling overall survival and its assumption that there was no further beneficial effect of vemurafenib on the risk of death.

4.11 The Committee discussed the costs associated with supporting BRAF V600 mutation testing. It heard from the clinical specialists that the test is currently being used in selected reference centres around the UK, with the cost of implementation supported by the manufacturer. The clinical specialists said that, although it can take weeks to provide a test result, the main time-limiting factor is accessing and preparing the tumour blocks, and transporting them, rather than performing the test. The Committee recognised the additional burden on pathology laboratories associated with vemurafenib treatment, but it was satisfied that BRAF V600 mutation testing is likely to become part of routine management for people with advanced melanoma and that it would not impose a significant resource impact on the NHS in the future.

4.12 The Committee noted that utility values in the manufacturer's model were sourced from the literature in the absence of robust data from the BRIM3 study. The Committee agreed with the manufacturer's assumption of a higher utility

value for progression-free survival for vemurafenib, given its improved clinical profile, including oral administration compared with intravenous administration for dacarbazine. The Committee noted that a utility of 0.59 was applied to the progressed disease state, which is lower than utilities for the same state accepted previously by the Committee for ipilimumab. It heard from the ERG that people who survive in the long term are likely to have a higher quality of life than those with rapidly progressive disease and therefore a higher utility for long-term survival (that is, survival greater than 5 years estimated to be 0.767) is justified. The Committee acknowledged the logic of this approach and was therefore persuaded that an improved utility value for the progressed disease state after 5 years of survival was justified.

4.13 The Committee considered the results of the manufacturer's updated cost-effectiveness analysis, which incorporated the ERG's suggested amendments (see sections 3.15 and 3.17) and the further errors identified in the economic model. The revised base-case deterministic ICER for vemurafenib compared with dacarbazine was £51,800 per QALY gained when the February 2012 data cut-off point (after RPSFT adjustment for switching) was used. The Committee was minded to compare the results of the RPSFT analysis with a scenario in which external data from trials of dacarbazine without switching to another drug was used (that is, Bedikian et al. [2011]). The Committee agreed that it was both a potential alternative method to evaluate the magnitude of the effect of switching and also a consistency check on direct methods such as the RPSFT. When the Bedikian trial data were used to model long-term survival with dacarbazine, rather than the RPSFT-adjusted BRIM3 trial data, the ICER was £44,400 per QALY gained using the February 2012 data cut-off point. The Committee concluded that, using the manufacturer's approach to modelling overall survival and the February 2012 data cut-off, the ICERs for vemurafenib compared with dacarbazine ranged between £44,000 and £51,800 per QALY gained.

4.14 The Committee considered the cost-effectiveness estimates for the additional scenario it had requested (see section 3.24). It was aware of the manufacturer's and the clinical specialists' opinions that such an analysis was inappropriate because the modelling approach gave a post-progression survival after treatment with vemurafenib that they considered to be implausible. The Committee noted that the ERG had undertaken the analysis as requested by the Committee, and this had resulted in an ICER for vemurafenib compared with dacarbazine of

£121,000 per QALY gained using the February 2012 data cut-off. The Committee then considered whether the ICERs presented by the manufacturer or the ICER from the Committee's requested scenario analysis were the more plausible. The Committee noted that it was unlikely that a single acceleration factor would capture the benefit of vemurafenib, which meant that the resulting ICER of £51,800 presented by the manufacturer should be interpreted with caution, although it accepted that the RPSFT method had been used in previous NICE technology appraisals. The Committee was satisfied with the use of external data, although there were concerns with reliability, and noted that the ICER calculated in this way was not inconsistent with, but was lower than, the RPSFT analysis that gave an ICER of £44,000 per QALY gained. The Committee was not satisfied that the alternative ICER (based on the Committee's requested scenario) of £121,000 per QALY gained represented the true benefit of vemurafenib because it accepted that it was implausible that post-progression survival after vemurafenib was shorter than after dacarbazine. The Committee therefore concluded that the most plausible ICER was in the range of £44,000 to £51,800 per QALY gained.

4.15 The Committee considered whether it would be appropriate to take into account sensitivity analyses on the discount rates used in the model and their effects on the revised ICER. It noted that a sensitivity analysis on the original base-case ICER, which included 3.5% discounting of costs and 1.5% discounting of benefits, gave an ICER of £48,200 per QALY gained. The Guide to the methods of technology appraisal (2008) clarification issued by the Board of NICE states that 'where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for health effects and 3.5% for costs'. Having referred to this clarification, the Committee considered that substantial restoration of health for a very long period equated to restoration of health to the extent that the person could be considered as having effectively been cured of their condition. The Committee noted that although there were patients in the vemurafenib arm of the BRIM3 study who showed a complete disease response, there was considerable uncertainty about how prolonged the benefit from the treatment would be. The Committee heard from the clinical specialists that there is no evidence at present to suggest that advanced melanoma is curable, or that vemurafenib would have substantial

benefits beyond 30 years. The Committee therefore concluded that there was no case for differential discounting to be applied.

4.16 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments which may extend the life of people with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

  In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.17 The Committee heard from the clinical specialists that the average life expectancy for people with locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma, particularly for those with distant metastases, as reflected in the trial population, was 3 to 9 months, and was unlikely to be greater than 24 months. The Committee also agreed that there was sufficient evidence from the BRIM3 study to indicate that treatment offers an extension to life of at least an additional 3 months, compared with current NHS treatment. The Committee heard from the manufacturer and the clinical specialists that the total number of people who would be eligible for treatment with vemurafenib was fewer than 1,000 each year in England and Wales, which the Committee accepted represents a small patient population. Therefore, the Committee was satisfied that vemurafenib met all the criteria for being a life-extending, end-of-life treatment and that the trial evidence presented for this was robust.

4.18 The Committee was aware that NICE's Guide to the methods of technology appraisal (2008) states that a strong case should be identified for accepting an ICER that is higher than £30,000 per QALY gained. The Committee noted that, in these circumstances, the NICE methods guide states that judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of:

- the degree of certainty around the ICER
- any strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured
- whether the innovative nature of the technology adds demonstrable and distinctive benefits of a substantial nature that may not have been adequately captured in the QALY measure.

Furthermore, the Committee was aware of NICE's response to Sir Ian Kennedy's report Appraising the value of innovation and other benefits, which states that, when considering a technology identified as having innovative characteristics, the Appraisal Committee should satisfy itself that:

- it can be regarded as a 'step-change' in the management of the condition, and
- either that the identified innovative characteristics have been taken into account in the QALY calculation (in other words, that their impact on health-related quality of life has been fully captured) or, if not, that they have been separately evaluated including their impact (if any) on the Committee's judgement of the most plausible ICER.

4.19 The Committee discussed whether the assessment of the change in health-related quality of life had been adequately captured in the economic analysis. It heard from a patient expert that successfully treated people could lead an active and fulfilling life and were able to contribute to society. The Committee accepted that vemurafenib represents a valuable new therapy and that its mechanism of action is novel. It acknowledged that few advances had been made in the treatment of advanced melanoma in recent years and vemurafenib could be considered a significant innovation for a disease with a high unmet clinical need. It also heard from the clinical specialists that vemurafenib had advanced the

understanding of this disease and opened the way to new treatments. The Committee considered that the symptomatic improvement attributable to vemurafenib had been captured in the higher utility value assigned to the progression-free survival health state for people receiving vemurafenib compared with dacarbazine. It considered that vemurafenib represents a highly effective new therapy in an area of unmet need; it has a novel mechanism of action, is a targeted therapy, is administered orally, is life-extending and meets the criteria for an end-of-life treatment. The Committee concluded that the combined value of these factors meant that vemurafenib could be considered a cost-effective use of NHS resources.

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 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

5.3 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.

5.4 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 locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma and the healthcare professional responsible for their care thinks that vemurafenib is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members, 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

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

Professor A E Ades
Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Professor Thanos Athanasiou (from September 2012)
Professor of Cardiovascular Sciences & Cardiac Surgery and Consultant Cardiothoracic Surgeon, Imperial College London and Imperial College Healthcare NHS Trust

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant
General Practitioner, Heartwood Medical Centre, Derbyshire

Dr Fiona Duncan
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr Andrew England (from September 2012)
Lecturer in Medical Imaging, NIHR Fellow, University of Liverpool

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

Professor Jonathan Grigg
Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Brian Hawkins (from September 2012)
Chief Pharmacist, Cwm Taf Health Board, South Wales

Dr Peter Heywood
Consultant Neurologist, Frenchay Hospital

Dr Sharon Saint Lamont
Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin
Consultant Endocrinologist, North Devon District Hospital

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 Alec Miners
Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Mohit Misra (from September 2012)
General Practitioner, Queen Elizabeth Hospital, London

Ms Sarah Parry (from September 2012)
CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees
Lay Member

Dr Ann Richardson
Lay Member

Dr Paul Robinson
Medical Director, Merck Sharp & Dohme

Ms Ellen Rule
Programme Director, NHS Bristol

Mr Stephen Sharp
Senior Statistician, MRC Epidemiology Unit

Dr Peter Sims
General Practitioner, Devon

Mrs Amelia Stecher
Associate Director of Individual Funding Requests and Clinical Effectiveness, NHS Kent and Medway

Mr David Thomson
Lay Member

Dr John Watkins
Clinical Senior Lecturer and Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Anthony S Wierzbicki (until September 2012)
Consultant in Metabolic Medicine and Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

Dr Olivia Wu
Reader in Health Economics, 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.

Kumar Perampaladas
Technical Lead

Fiona Rinaldi (until August 2012) and Nicola Hay (from August 2012)
Technical Advisers

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:

- Dickson R, Bagust A, Beale S et al. Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation positive malignant melanoma: A Single Technology Appraisal. Liverpool Reviews and Implementation Group, 2012.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were also invited to comment on the appraisal consultation documents. Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Roche Products (vemurafenib)

Professional or specialist and patient or carer groups:

- British Association of Dermatologists
- British Association of Skin Cancer Nurse Specialists
- Factor 50
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians (NCRI, RCP, RCR, ACP, JCCO)
- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health
- NHS Birmingham East and North
- Welsh Assembly Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Bayer (dacarbazine)
- Bristol-Myers Squibb (ipilimumab)
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Improvement Scotland
- Liverpool Reviews & Implementation Group, University of Liverpool
- National Collaborating Centre for Cancer
- National Institute for Health Research Health Technology Assessment Programme

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on vemurafenib by attending the Committee discussions and providing written evidence to the Committee. They were also invited to comment on the appraisal consultation documents.

- Dr Louise Fearfield, Consultant Dermatologist, nominated by an organisation representing the British Association of Dermatologists – clinical specialist
- Dr Paul Lorigan, Senior Lecturer in Medical Oncology, nominated by and organisation representing Roche and Royal College of Physicians – clinical specialist
- Professor Martin Gore, Consultant Medical Oncologist nominated by an organisation representing the Royal College of Physicians – clinical specialist
- Mrs Gillian Nuttall, CEO and Founder, nominated by an organisation representing Factor 50 – patient expert

- Mr Steve Chalk, nominated by an organisation representing Factor 50 – patient expert

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

- Roche Products

Update information

January 2015: Before 1 January 2015, the manufacturer made BRAF V600 mutation testing available free of charge by funding 3 BRAF reference testing centres in the UK. This funding has now been withdrawn and references to it in this document have been removed.

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