NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Changes to the study design and data analysis for the BRIM3 study were needed as the study progressed, including a change in the primary outcome measure and allowing the cross-over of patients from the dacarbazine (comparator) group. What is the Committee's view on the impact of these changes on the way the findings are interpreted and subsequently incorporated into the economic modelling?
- Three analyses of the BRIM-3 dataset are available. Which analysis does the Committee consider to be the most plausible for determining the long-term effects of vemurafenib therapy?
- Does the Committee consider that there is any evidence to support the development of resistance to vemurafenib during treatment, and if so, is the clinical effectiveness of vemurafenib likely to substantially differ from that seen in the BRIM3 study in routine clinical practice?

- Does the Committee consider that there are significant resource implications likely to be associated with routine BRAF V600 mutation testing?

Cost effectiveness

- Does the Committee consider that the March 2011 data cut-off of the BRIM3 study was the most appropriate to use as the basis for economic modelling, given that an additional 6 months of data (October 2011 cut-off) were available from the study for overall survival estimates?
- Does the Committee consider the manufacturer's assumption that vemurafenib continues to yield survival gains once treatment has stopped (that is, after disease progression) to be reasonable?
- In the absence of long-term data from the BRIM3 study, the manufacturer modelled overall survival using three sources and six different phases to derive survival estimates. Does the Committee consider this approach to be robust?
- The ERG considered that the utility assumed for long-term survivors (0.59) in the manufacturer's model is an underestimate. What is the Committee's view?
- The ERG noted that the manufacturer did not include a disutility associated with adverse events that lead to a dose reduction, and therefore recognised that the progression-free survival benefit may be optimistic. What is the Committee's view on the impact of not including disutility associated with adverse events in the model?
- The manufacturer made a case in its submission that discount rates that are lower than the reference case should be applied to vemurafenib. Does the Committee agree that vemurafenib meets NICE's supplementary criteria for differential discounting to be applied?

Other

- Does the Committee consider that there are any benefits of vemurafenib treatment that have not been adequately captured in the QALY calculation?
- Does the Committee consider that vemurafenib is a life-extending treatment that fulfils the criteria in the supplementary advice on end-of-life treatments?

  Does the Committee consider that there any equality issues that should be taken into account?

1 Background: clinical need and practice

1.1 Cutaneous melanoma is a malignant tumour of the skin. Melanoma can spread to nearby lymph nodes (stage III) or to other parts of the body (stage IV). People with an above-average mole count, sun-sensitive skin or a strong family history of melanoma are at increased risk.

1.2 The incidence of malignant melanoma is increasing in the UK. In 2008, there were 11,767 new cases of malignant melanoma diagnosed in the UK, and 2067 related deaths. The manufacturer estimates that approximately 850 people per year will be eligible to receive vemurafenib. In the UK, melanoma is diagnosed at a mean age of around 50 years but up to 20% of cases occur in young adults aged between 15 and 39 years. For people with metastatic malignant (stage IV) disease, median survival is approximately 6–9 months.

1.3 Early recognition of malignant melanoma and accurate diagnosis present the best opportunity for cure by surgical resection of the tumour. A very small minority of people with advanced disease can still have their tumour removed. Unresectable stage III or IV (metastatic) disease is usually managed by a specialist oncologist

and first-line standard care usually involves dacarbazine. Radiotherapy, immunotherapy and combination chemotherapy have also been studied in randomised clinical trials. Limited treatment options are currently available for second- or subsequent-line therapy.

1.4 UK clinicians have noted that tumour shrinkage while receiving vemurafenib has a positive impact on quality of life of a magnitude that is 'rare with conventional chemotherapy'.

2 The technology

2.1 Vemurafenib (Zelboraf, Roche Products) has a UK marketing authorisation for 'the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma'. Vemurafenib is an oral tyrosine kinase inhibitor that selectively inhibits the mutated BRAF enzyme, which is found in about half of malignant melanomas and is responsible for abnormal cell survival. The recommended dose of vemurafenib is 960 mg (four 240-mg tablets) twice daily (equivalent to a total daily dose of 1920 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'. For further information see the summary of product characteristics. Vemurafenib has been available since June 2011 in 12 centres in the UK through an expanded access programme. Approximately 200 patients have received treatment through this programme to date.

2.2 In order to receive treatment with vemurafenib, a BRAF V600 mutation test is needed. Vemurafenib was co-developed with the Roche cobas 4800 BRAF V600 mutation test, which is commercially available in the European Union. The manufacturer

anticipates that BRAF V600 mutation testing of all people with advanced melanoma will become standard clinical practice in the UK and is currently supporting three BRAF reference testing centres (Institute of Cancer Research, Surrey; Queen Elizabeth Hospital, Birmingham; Saint Mary's Hospital, Manchester) free of charge.

2.3 The summary of product characteristics lists the following as the most common adverse reactions associated with vemurafenib treatment: arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus. Treatment with vemurafenib is also associated with the formation of cutaneous squamous cell carcinomas. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The list price of vemurafenib is £1750 for one pack of 56 x 240-mg tablets (1 week's supply) (excluding VAT; 'Monthly Index of Medical Specialities' [MIMS] May 2012). The manufacturer has estimated that the average cost of vemurafenib would be [redacted] per patient for a course of treatment (assuming an average length of treatment is 7 months). Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of vemurafenib within its licensed indication for the treatment of unresectable locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with unresectable locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma	A narrower population has been considered – that is, only people who are treatment naive. Cost-effectiveness analyses for people with previously treated malignant melanoma were not presented by manufacturer. The manufacturer stated 'due to a lack of RCT or historical control data on the outcomes experienced by previously treated BRAF V600 mutation positive patients and the magnitude of the ICERs estimated in the previously untreated model (£89,613/QALY and above) and the significant uncertainty associated with the setting in which RCT data was available, a complete decision analytic model investigating the cost-effectiveness of vemurafenib as a second-line treatment based upon the single arm BRIM2 study (inherently subject to more uncertainty) has not been constructed and it does not appear possible to robustly demonstrate that vemurafenib should be considered cost-effective in this setting'.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year		

3.2 The ERG highlighted that the manufacturer presented information on people with BRAF V600 mutation-positive melanoma who have not previously received treatment, which is in contrast to the original decision problem which allowed for vemurafenib to be considered in both first- and subsequent-line treatment settings.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Vemurafenib	As per scope
Comparators	For people with previously untreated malignant melanoma: • dacarbazine. For people with previously treated malignant melanoma: • ipilimumab (subject to ongoing NICE technology appraisal). • best supportive care.	As per scope for previously untreated melanoma. People with previously treated malignant melanoma were not considered in the manufacturer's submission, so comparisons with ipilimumab and best supportive care were not presented.

3.3 The ERG noted that the manufacturer appropriately followed the decision problem in the first-line treatment setting, and used dacarbazine as the comparator.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	As per scope

3.4 Data for overall survival, progression-free survival, response rates (reported as best overall response) and adverse events were available from the clinical trials and were presented by the manufacturer. The primary endpoint for 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 Food and Drug Administration.

3.5 The ERG noted the absence of health-related quality of life data from a validated, preference-based measure. Although the manufacturer collected health-related quality of life data using the

functional assessment of cancer therapy-melanoma (FACT-M) questionnaire during the BRIM3 study, results were not presented because completion rates were low, and the manufacturer considered that the FACT-M questionnaire did not conform to the NICE reference case. [redacted]

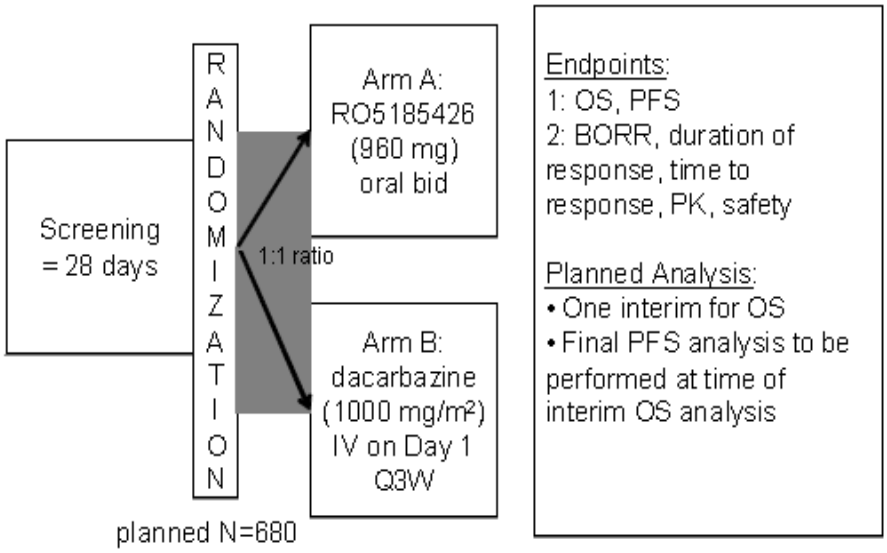
	Final scope issued by NICE	**Decision problem addressed in the submission**
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope
Subgroups to be considered	None	As per BRIM3 trial

4 Clinical-effectiveness evidence

4.1 The manufacturer carried out a search of the literature to identify studies investigating the efficacy of vemurafenib in the treatment of unresectable locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. The key clinical evidence came from one multicentre randomised phase III trial (BRIM3).

4.2 BRIM3 is an international, randomised, unblinded, open-label, active-controlled trial that compared vemurafenib (960 mg twice daily orally; n = 337) with dacarbazine (1000 mg per square metre of body-surface area by intravenous infusion every 3 weeks; n = 338) in patients with previously untreated stage IIIc or IV BRAF V600 mutation-positive metastatic melanoma until disease progression or unacceptable toxicity. Details of the study design are summarised in figure 1.

Figure 1 BRIM3 study design and endpoint summary



Stratification factors at randomization included: metastatic disease stage classification, ECOG performance status, LDH level, and geographic region.
BORR = best overall response rate; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics.

Source: manufacturer's submission page 48

4.3 The randomisation process produced equivalent-sized groups, however 14% of patients (48 of 338) randomised to receive dacarbazine did not receive treatment, primarily because of withdrawal of consent or refusal of treatment. It is unclear what impact this may have had on data analysis of the trial populations or if it led to any imbalances in the baseline characteristics between the treatment groups.

4.4 The co-primary outcomes in the BRIM3 study were overall survival and progression-free survival (figure 1). Secondary outcomes included assessment of vemurafenib using confirmed best overall response rate (BORR), duration of response and time to response. Results presented in this report are for the intention-to-treat populations, except where indicated.

4.5 Three separate analyses for overall survival were completed based on three different data cut-off points (December 2010, March 2011 and October 2011; see table 1). The data safety monitoring board recommended the release of the interim results on compelling efficacy based on the review of the results of the planned interim analysis of overall survival, and the study was ended and cross-over permitted at this time (December 2010). This dataset was used to support US and European Medicines Agency regulatory submissions, because sufficient data on progression-free survival were available. Two additional analyses have been performed by the manufacturer (using March 2011 and October 2011 data cut-off time periods) to demonstrate the survival benefit conferred by vemurafenib during follow up. No formal hypothesis testing occurred after cross-over was permitted, because statistical significance of the overall survival benefit had been demonstrated based on the December 2010 data cut-off time point. The analyses completed at different data cut-off points are reported in table 1.

Table 1 Summary of analyses performed for BRIM3 study

Data cut-off	Analyses performed	Reason for analysis
30 December 2010	Interim analysis of OS, final analysis of PFS, analysis of secondary outcomes, subgroup analyses, sensitivity analyses	Planned interim analysis – based on compelling results DSMB recommended release of results so full analyses were performed on this data set.
31 March 2011	Update of OS, PFS and safety analyses – no formal hypothesis testing occurred	Health authority (FDA)request for further follow-up data to be included
3 October 2011	Update of OS – no formal hypothesis testing occurred	Health authority request for further follow-up data to be included
DSMB, Data and Safety Monitoring Board; FDA, US Food and Drug Administration; OS, overall survival; PFS, progression-free survival Source: Evidence Review Group report, table 8, page 26		

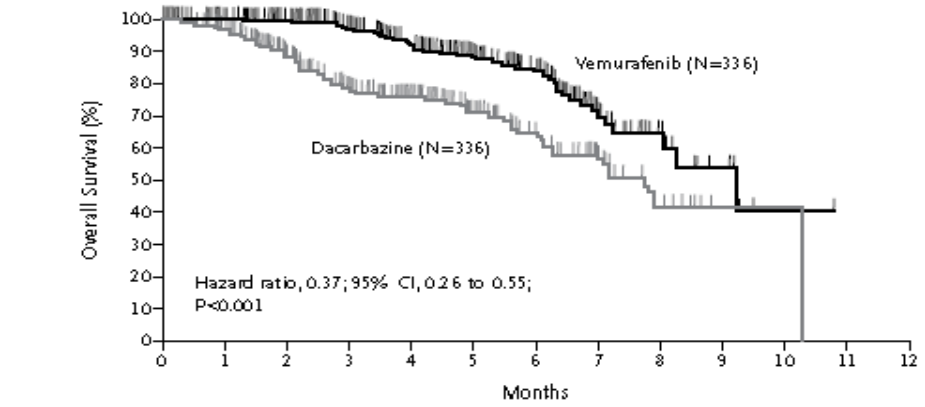
4.6 Results from the planned interim analysis (December 2010 data cut-off; table 2) of the BRIM3 trial showed that treatment with vemurafenib led to a statistically significant reduction in death (hazard ratio [HR] 0.37; 95% confidence interval [CI] 0.26 to 0.55; $p < 0.001$). At 6 months, overall survival 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 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 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 (evaluated in 549 patients). See figures 8 and 10 on pages 83–85 of the manufacturer's submission and figure 2 in this document for further details of the results for overall survival and progression-free survival.

Table 2 Summary of results for BRIM3 study

December 2010 data cut-off		**Vemurafenib**	**Dacarbazine**
Primary comparison		N = 337	N = 338
PFS	Hazard ratio	0.26 (0.20, 0.33)	
(n = 549)	Median PFS, months (95% CI)	5.32 (4.86 to 6.57)	1.61 (1.58 to 1.74)
OS	Hazard ratio	0.37 (0.26, 0.55)	
	Number of deaths (%)	43 (13%)	75(22%)
Secondary comparison		N = 219	N = 220
Confirmed response rate % (95% CI) (106/219 evaluable patients for vemurafenib; 12/220 evaluable patients for dacarbazine)		48% (42 to 55)	5% (3 to 9)
Duration of response (months)		5.49 (1.22 to 7.62)	Not reached
Median time to response (months)		1.45	2.7
March 2011 data cut-off			
OS at 6 months (%, 95% CI)		84 (78 to 89)	64 (56 to 73)
OS	Hazard ratio	0.44 (0.33, 0.59)*	
	Number of deaths (%)	78 (23%)	122 (36%)
Number of cross-over patients: 50 (15%)			
October 2011 data cut-off			
Median OS (months)		13.2	9.6
OS	Hazard ratio	0.62 (0.49, 0.77)*	
	Number of deaths (%)	159 (47)	175 (52)
Number of cross-over patients: 81 (24%)			
CI, confidence interval; OS, overall survival; PFS, progression-free survival * censored results at time of cross-over; non-censored results at time of cross-over: 31 March HR = 0.47 (95% CI 0.35 to 0.62) and 3 October HR = 0.67 (95% CI 0.54 to 0.84) Source: Manufacturer's submission pages 80 and 87			

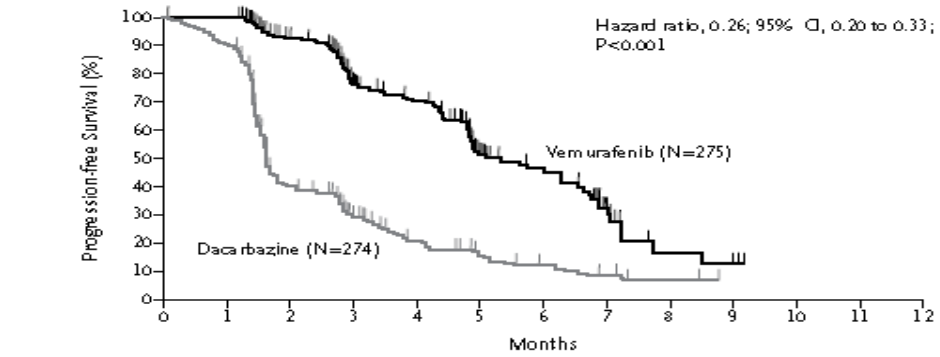
Figure 2 Overall survival (A) and progression-free survival (B) based on December 2010 data cut-off of BRIM3 study

A. Overall survival



No. at Risk												
Dacarbazine	336	283	192	137	98	64	39	20	9	1	1	0	0
Vemurafenib	336	320	266	210	162	111	80	35	14	6	1	0	0

B. Progression-free survival

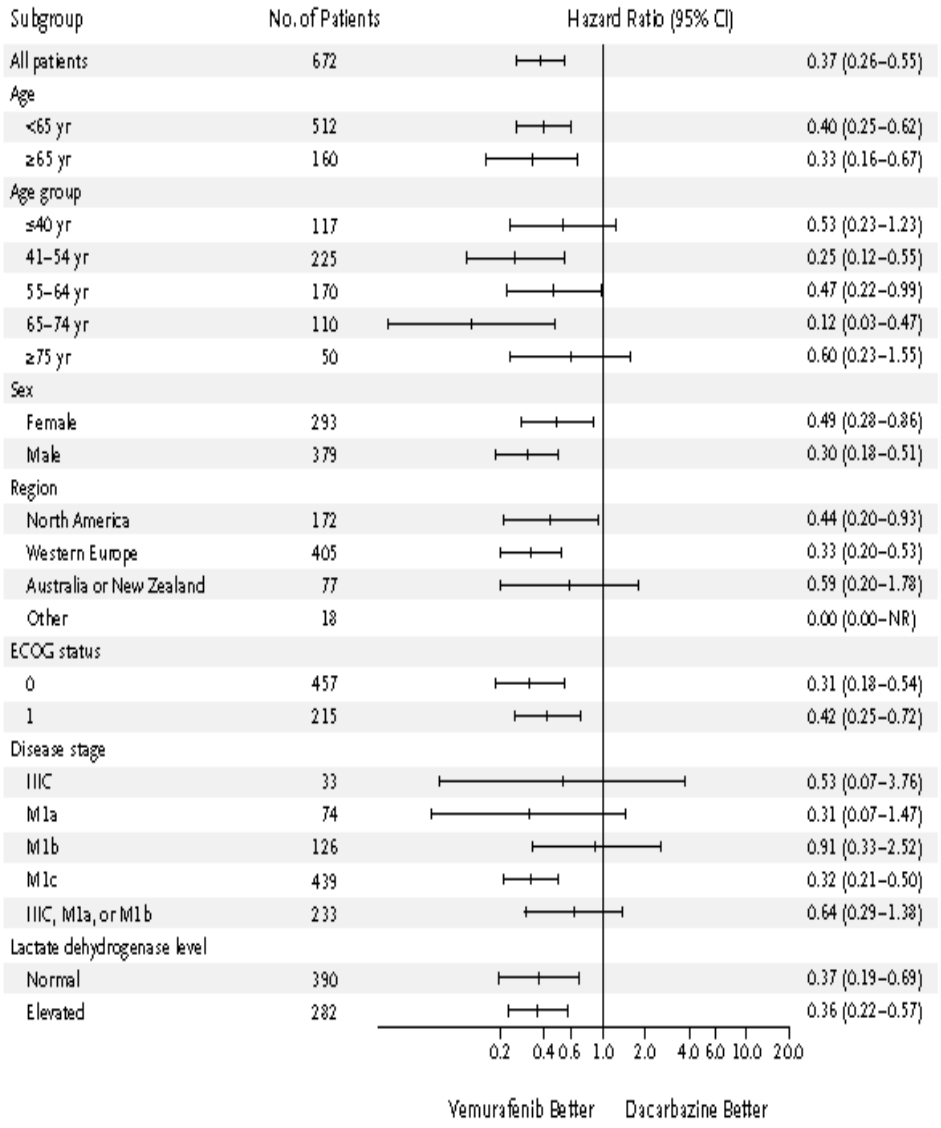


No. at Risk												
Dacarbazine	274	213	85	48	28	16	10	6	3	0	0	0	0
Vemurafenib	275	268	211	122	105	50	35	16	4	3	0	0	0

Source: manufacturer's submission pages 83 and 84

4.7 A range of pre-specified subgroups were reported by the manufacturer, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, tumour stage and geographical regions. The results showed that the survival benefit conferred by vemurafenib treatment was generally maintained across subgroups. See figure 3 for details of the results of the pre-specified subgroups.

Figure 3 Sub-group analyses for interim analysis of overall survival from BRIM3 study



Source: page 84 of manufacturer's submission

ECOG, Eastern Cooperative Oncology Group

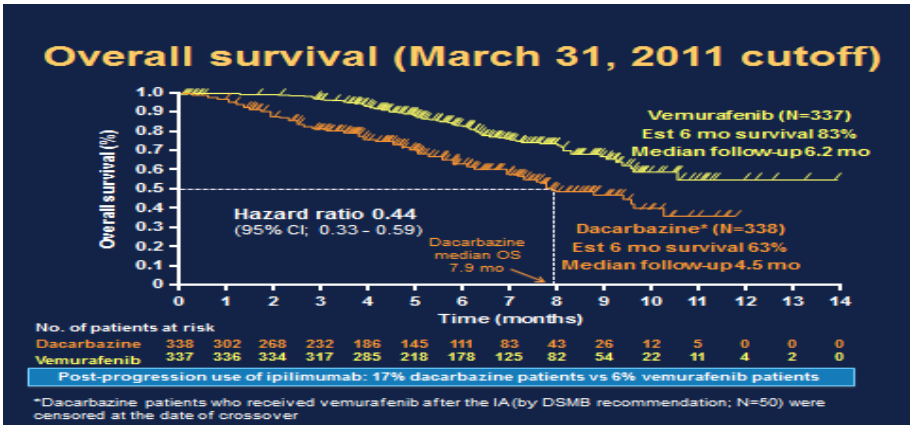
4.8 The secondary outcome of confirmed tumour response could be calculated for 439 patients at interim analysis (on the basis of having undergone randomisation less than 14 weeks before the clinical cut-off date of December 2010). In the vemurafenib treatment group, 106 of 219 patients (48%; 95% CI 42 to 55) had a

confirmed objective response (including two 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 (see table 2).

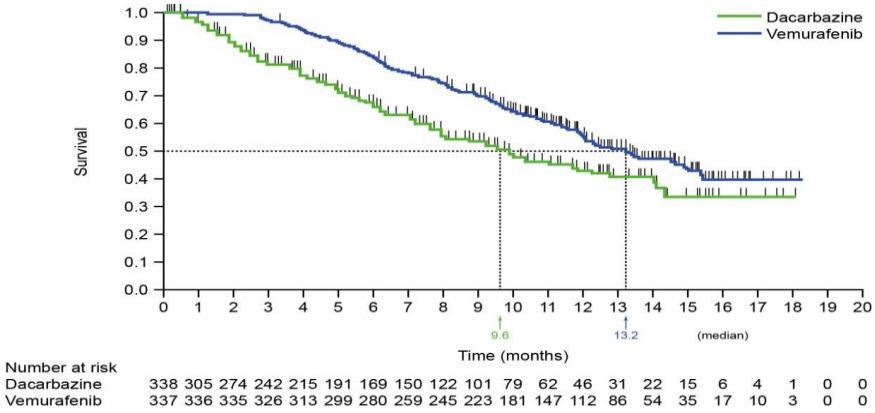
4.9 Results from an analysis using the March 2011 data cut-off showed that median overall survival was only reached for the dacarbazine group (median overall survival 7.9 months; HR 0.44; 95% CI 0.33 to 0.59). Results from the October 2011 data cut-off showed that median overall survival was 13.2 months for the vemurafenib group and 9.6 months for people treated with dacarbazine. Figure 4 shows updated Kaplan-Meier estimates from the manufacturer for overall survival using the March and October 2011 data cut-off points.

Figure 4 Updated results for Kaplan-Meier estimates of overall survival using March (A) and October 2011 (B) data cut-off points

A. March 2011



B. October 2011



Source: manufacturer's submission pages 86 and 87

4.10 The manufacturer reported adverse events (grade 2 or more) from the BRIM3 study using the December 2010 data cut-off point. A total of 618 patients were evaluated for toxic effects. Treatment-related adverse events were recorded for more patients who received vemurafenib because they stayed on treatment longer than those who received dacarbazine. The most common adverse events in the vemurafenib group were cutaneous events, arthralgia, and fatigue. Photosensitivity skin reactions of grade 2 or 3 severity were seen in 12% of patients. People treated with dacarbazine experienced fatigue, nausea, vomiting and neutropenia. A total of 42 patients (13%) in the vemurafenib group died during the course of the study compared with 66 patients in the dacarbazine group. The most common cause of death in both groups was disease progression.

4.11 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. The overall incidence of grade 4 (life-threatening) adverse events was lower in the vemurafenib group than the dacarbazine group (13 compared with 22 patients).

4.12 As of 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. Adverse events that led to discontinuation were higher in patients treated with vemurafenib than with dacarbazine (88 patients compared with 15). See table 3 below and tables 25 and 26 on page 124 of the manufacturer's submission for more details.

Table 3 BRIM3 study summary of adverse events and deaths

Adverse events – Feb 2011 (CSR)*	**Vemurafenib n = 336**	**Dacarbazine n = 282**
	Number (%) of patients	Number (%) of patients
Patients with at least one dose modification (reduction or interruption)	159 (47.3)	44 (15.2)
Reasons:		
Dose adjusted per protocol	92 (27.4)	–
Non-compliance	26 (7.7)	–
Other	136 (40.5)	13 (4.5)
Adverse event	–	25 (8.7)
Adverse events – December 2010 data cut-off		
Any adverse events	326 (97)	253 (90)
Adverse events of grade 3 and above	168 (50)	86 (30)
Adverse events of grade 3	163 (49)	74 (26)
Adverse events of grade 4	13 (4)	22 (8)
Adverse events of grade 5	6 (2)	6 (2)
Deaths†	42** (13)	66** (23)
Deaths within 28 days of last dose of study drug†	22 (6.5)	16 (5.5
Serious adverse events	110 (33)	45 (16)
Drug-related adverse events	316 (94)	194 (69
Drug-related serious adverse events	88 (26)	15 (5)
Adverse events that led to withdrawal from treatment***	19(6)	12 (4)
Adverse events that led to dose modification/interruption	129(38)	44 (16)

* The final database for the purpose of the CSR was obtained on February 7, 2011, with updated adverse events and laboratory obtained on February 28 and April 1, 2011, respectively (source: manufacturer's submission page 44)

**In the dacarbazine group, 63 of the 66 deaths were due to disease progression; in the vemurafenib group, 35 of the 42 deaths were due to disease progression.

*** Source: CHMP assessment report table 34, page 72

† Deaths were based on the all-treated population, where the N = 289 for dacarbazine and N = 336 for vemurafenib.

Source: Manufacturer's submission pages 124 and 125; Evidence Review Group report page 32

Evidence Review Group comments

4.13 Overall, the ERG considered that the BRIM3 trial was well-designed and that the clinical effectiveness evidence presented by

the manufacturer was broadly relevant to the decision problem. The ERG considered that data from the BRIM3 study demonstrate a statistically significant difference for both overall survival and progression-free survival for vemurafenib over dacarbazine in patients with locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma who had not received previous treatment. The ERG raised some concerns about the clinical effectiveness evidence in the manufacturer's submission:

- The ERG raised concerns with the statistical approach adopted for the co-primary endpoints of progression-free survival and overall survival. Because the manufacturer's decision to include progression-free survival as a co-primary endpoint was made following advice from the US Food and Drug Administration, the sample size calculation had to be revised. [redacted]
- The ERG cautioned that the short-term nature of the results from the BRIM3 study and the heterogeneity of the patient population impose substantial uncertainty on the projection of long-term benefits of treatment.
- The ERG noted that a number of exploratory and subgroup analyses were originally planned but subsequently not reported by the manufacturer.
- The ERG noted that the health-related quality of life data collected in the BRIM3 study using the FACT-M questionnaire were not reported, and stratified analyses of overall survival and

progression-free survival were performed but not reported in the manufacturer's submission.

- The ERG acknowledged the manufacturer's concern that caution should be exercised when comparing the adverse events associated with vemurafenib and dacarbazine because the treatment duration with vemurafenib was much longer than with dacarbazine (3.1 months compared with 0.76 months for dacarbazine; based on the December 2010 data cut-off).
- The ERG noted that dose modification was needed in 159 (47%) of patients treated with vemurafenib and, of these, 112 patients (33%) had at least one dose reduction and 147 (44%) had one or more dose interruptions because of an adverse event (CSR – Feb 2011). The mean number of days for such interruptions was 8 (range 1–38 days). Clinical advisors to the ERG agreed with the manufacturer's interpretation that dose modifications and interruptions are manageable because treatment with vemurafenib is associated with rapid tumour response and symptomatic relief.

5 Comments from other consultees

5.1 Clinical specialists noted that vemurafenib is likely to replace dacarbazine as standard treatment for locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma because dacarbazine, although well tolerated, is not considered to be very effective. Clinical specialists estimate that approximately 40–50% of patients with malignant melanoma will be positive for the BRAF V600 mutation, and expect treatment to be carried out in secondary or specialist oncology clinics. Further, dacarbazine is administered intravenously, necessitating visits to the hospital, and is often administered with prophylactic anti-emetics. Vemurafenib on the other hand is an oral formulation, and the main side effects

on the skin and joints can be managed with dose reductions and standard topical treatments. Therefore, vemurafenib represents an important new therapy in the management of unresectable malignant melanomas.

5.2 Clinical specialists also noted that a guideline on the management of skin toxicities associated with vemurafenib treatment is currently being prepared. They also noted that the technology used to test for BRAF V600 mutations is not dissimilar to the technology used to screen for epidermal growth factor receptor (EGFR) mutations, and noted that BRAF V600 mutational analysis has benefits in terms of improving patient survival and reducing adverse events and costs.

5.3 Patient experts noted that once the side effects of treatment are managed, vemurafenib results in improved quality of life, mental health and patient satisfaction. Patients noted that additional benefits of vemurafenib treatment include improved self-esteem, improved family relationships and the ability to return to work.

6 Cost-effectiveness evidence

Manufacturer's submission

6.1 The manufacturer presented a de novo economic model for the economic evaluation of vemurafenib for the first-line treatment of adults with BRAF V600 mutation-positive metastatic malignant melanoma. The manufacturer noted that it was not possible to present a robust case to demonstrate that vemurafenib is cost effective as a second-line treatment because of the absence of clinical evidence for this patient population.

6.2 The model comprised three health states: progression-free survival, progressed disease and death. All patients entered the model in the progression-free survival health state and either remained in

progression-free survival or progressed to a worse health state (that is, progressed disease or death). The model relied on the BRIM3 trial to derive the mean age and body weight of patients, as well as average treatment durations for vemurafenib (that is, a dose of eight 240-mg tablets daily and 56 tablets dispensed every 28 days unless dose is reduced because of adverse events) and dacarbazine (that is, a dose of 1000 mg per square metre of body-surface area by intravenous infusion every 3 weeks). The average cycle length was 1 week, and the model was reviewed by independent clinical specialists. The model incorporated differential utility values derived for each treatment depending on the response rate observed (see 6.5-6.7). Administration costs for dacarbazine were taken from NHS Reference costs 2009/2010. The time horizon is set at 30 years, and a discount rate of 3.5% was applied to both costs and benefits.

6.3 The manufacturer reported that the cost of a BRAF V600 diagnostic test is £95, which produces an estimated cost of £197.92 per BRAF V600-positive patient identified (that is, a 48% mutation rate was used as reported by Long et al. [2010]). A cost of £63.30 for dacarbazine (2 x 1000-mg vials) was used in the model and was based on the average body surface area reported in the BRIM3 trial. Table 4 reports the intervention and comparator drug costs.

Table 4 Summary of inputs used in manufacturer's economic model

Costs	Value	CI	References in manufacturer's submission
Pharmacy costs per dispensing state	£13 every 4 weeks	£6.63, £19.37	Section 6.5.5
BRAF testing cost	£95 (£197.92 per BRAF V600 mutation-positive patient identified)		Section 6.5.5
PFS BSC	£378 per month	£192.78, £563.22*	Section 6.5.6
PD BSC	£378 per month	£192.78, £563.22*	Section 6.5.6
Terminal care cost	£5,408 one off	£2755; £8047*	Section 6.5.6
Cost on PD	£648 one off	£330, £965.52*	Section 6.5.6
Palliative care (4 months before death)	£838 per month	£427.38, £1,248.62*	Section 6.5.6
Dacarbazine administration	£248	£126, £369.52*	Section 6.5.5
Cost of rash	£126.96	£64.75, £189.17*	Section 6.5.7
Cost of neutropenia	£407.38	£207.76, £607.00*	Section 6.5.7
Cost of CuSCC/ keratocanthoma	£115	£58.65, £171.35*	Section 6.5.7
Cost per pack of vemurafenib	£1750 (56 tablets)		Section 6.5.5
Cost per dose of dacarbazine	£63.50		Section 6.5.5

Source: manufacturer's submission page 184

* Gamma distribution applied under assumption standard error was a quarter of base-case value.

BSC, best supportive care; CI, confidence interval; CuSCC, cutaneous squamous cell carcinoma; PD, progressed disease; PFS, progression-free survival

6.4 The model relied on the March 2011 data cut-off to derive treatment effects, where cross-over was 7%. For progression-free survival, the model used the probability of remaining in progression-free survival observed in the BRIM3 trial until month 9 for vemurafenib and month 7 for dacarbazine, after which survival for each intervention was extrapolated using exponential functions.

The progression-free survival monthly hazard curve tail is 0.2087 for vemurafenib and 0.2437 for dacarbazine.

6.5 Overall survival in the dacarbazine arm was based on the three different sets of data. The probability of overall survival in the BRIM3 trial was used directly for 40 weeks (9.2 months), with the longer-term outcomes derived from the Robert et al (2011) trial data (months 1–14; months 14–23; months 23–35; and months 35–46) with different functions fitted to allow for a decreasing hazard to be estimated for each of these intervals. For months 46 and beyond, a hazard estimate taken from the surveillance, epidemiology and end results (SEER) registry was used.

6.6 The vemurafenib arm used the probability of overall survival observed in the BRIM3 trial directly for the first 9.5 months and a hazard ratio representing the differences between the vemurafenib and dacarbazine arms up to month 14, after which the manufacturer assumed that vemurafenib provided no further treatment benefit. Details of the model variables are available in table 5.

Table 5 Summary of parameters used in the model

Parameter	Value	Distribution	Reference
Age	54 years		BRIM3 RCT
BRAF V600 mutation rate	48%		Long et al. 2010
Response rate (vemurafenib)	48.4%	42%, 55% (normal)	BRIM3 RCT
Response rate (dacarbazine)	5.5%	3%, 9% (normal)	BRIM3 RCT
Utility values			
PFS vemurafenib	0.806	Not derived	Derived using reported values [a], [b] and [c] below (manufacturer's submission page 197)
PFS dacarbazine	0.767	Not derived	Derived using reported values [a], [b] and [d] below (manufacturer's submission page 197)
PD	0.59	0.57 to 0.602	Beusterien et al. 2009
Reported values			
PFS (response) [a]	0.85	0.833 to 0.867	Beusterien et al. 2009
PFS (stable disease) [b]	0.77	0.755 to 0.785	Beusterien et al. 2009
Skin reaction (rash) [c]	-0.03	-0.0296 to -0.0304	Beusterien et al. 2009
Neutropenia [d]	-0.08973	-0.088 to -0.092	Nafees et al. 2008
PFS monthly hazard in curve tail			
Vemurafenib		0.2087	Section 6.3.1 of the manufacturer's submission
Dacarbazine		0.2437	
Overall survival monthly hazard in curve tail			
9–14 months	Vemurafenib	0.0761	
	Dacarbazine	0.0855	
14–23 months	Vemurafenib and dacarbazine	0.0658	
23–35 months	Vemurafenib and dacarbazine	0.0328	
35–46 months	Vemurafenib and dacarbazine	0.0141	
46 months onwards	Vemurafenib and dacarbazine	0.001905	

PD: progressed disease; PFS, progression-free survival; OS;, overall survival; RCT, randomised controlled trial

Source: manufacturer's submission page 181 and Evidence Review Group page 40

6.7 The manufacturer used utility values from a study by Beusterien et al (2009), in line with values used in the ongoing NICE technology appraisal 'Ipilimumab for previously treated unresectable stage III or IV malignant melanoma' (publication date to be confirmed). Utility values from Beusterien et al were combined with disutility values associated with adverse events to generate utility values for the model. Utility values are shown in table 5.

6.8 The base-case results included all drug acquisition costs, resources associated with administration and testing, and costs associated with adverse events. Treatment with vemurafenib compared with dacarbazine demonstrated an incremental cost-effectiveness ratio (ICER) of £94,267 per QALY gained and £64,891 per life-year gained. The manufacturer also undertook a probabilistic sensitivity analysis to estimate the mean ICER of vemurafenib compared with dacarbazine. There was a 0% chance of vemurafenib being cost effective if the maximum acceptable ICER was £85,000 per QALY gained; if the maximum acceptable ICER was £100,000 per QALY gained vemurafenib would be considered cost effective in 96.9% of simulations. The base-case results, along with predicted resource use by category, are presented in tables 6 and 7.

Table 6 Manufacturer's base-case results

Technology	Total			Incremental			ICER (incremental cost per QALY)
	Costs	Life-years gained	QALYs	Costs	Life-years gained	QALYs	
Dacarbazine	[redacted]	[redacted]	[redacted]				
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,267

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 7 Summary of resource usage by category for manufacturer's base-case

Unit cost	Vemurafenib	Dacarbazine	Increment	Absolute increment	% absolute increment
Drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pharmacy/ administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRAF V600 testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event; BSC, best supportive care; PD, progressed disease; PFS, progression-free survival
Source: Evidence Review Group report page 44

6.9 The manufacturer undertook a series of one-way deterministic sensitivity analyses to test the robustness of the results by varying most of the parameters used in the economic evaluation, including transition probabilities (± 10%), utilities (± 10%), costs (based on upper and lower 8% confidence interval assuming the standard error = 0.24 base-case value). Patient characteristics (± 10%) and BRAF V600 mutation incidence (40–60%) were also varied. The results indicated that vemurafenib was most sensitive to discount rates and variations to the hazard of death between months 9 and 14. Results are shown in table 8.

Table 8 Manufacturer's deterministic sensitivity analysis results

Description	Summary of results
(1) Health outcome discounting (0–6%)	ICER ranges from £70,358 (0%) to £110,535 (6%)
(2) Monthly hazard of death (vemurafenib) (months 9–14)	ICER ranges from £87,279 (-10%) to £102,283 (+10%)
(3) Monthly hazard of death (dacarbazine) (months 9–14)	ICER ranges from £100,775 (-10%) to £88,808 (+10%)
(4) Time horizon	ICER reduces to £103,793 with 20-year time horizon
(5) Monthly hazard of death (both), (months 14–23)	ICER ranges from £90,977 (-10%) to £97,618 (+10%)
(6) Costs discount rate	ICER ranges from £98,346 (0%) to £92,178 (6%)
Both discount rates	ICER ranges from £73,397(0%) to £108,090 (6%)
(7) Resultant PFS utility values	Dacarbazine (0.767) to both arms: ICER £98,339; Vemurafenib (0.806) to both arms: ICER £96,070
(8) Age	ICER ranges from £93,071 (average = 45) to £94,584 (average = 65)
(9) Monthly hazard of death (both) (months 23–45)	ICER ranges from £92,290 (-10%) to £96,258 (+10%)
ICER, incremental cost-effectiveness ratio; PFS, progression-free survival	
Source: Evidence Review Group report page 45	

6.10 The manufacturer highlighted that overall survival was not varied in probabilistic sensitivity analyses because it was not possible to determine which extrapolation approach should be given a higher likelihood of occurring. The manufacturer concluded that the results of the probabilistic sensitivity analyses significantly understate the uncertainty associated with the incremental QALY gained for vemurafenib.

6.11 The manufacturer also provided additional scenario analyses that used different estimates for utility and treatment effects (see table 9).

Table 9 Manufacturer's scenario analyses results

Description	Summary of results (ICERs)
Base case	£94,267
Overall survival	
Overall survival from October 2011 data cut-off (A)	£128,060
Base case with 34-month treatment effect (B)	£77,343
Utility estimates	
Base case with higher Hodi mapped PD value used to reflect the potential for patients in 'tail' of survival curve to have lower tumour burden and therefore improved health-related quality of life (C)	£82,017
Hodi EORTC-QLQ-C30 mapped values (PFS: 0.80; PD:0.76) (D)	£83,643
Hodi SF-36 mapped values (PFS: 0.64; PD:0.62) (E)	£103,345
B+C	£65,747
B+C; discount rate of 0% to health outcomes	£46,524
EORTC, European Organisation for Research and Treatment of Cancer; PD, progressed disease; PFS, progression-free survival, QLQ, quality of life questionnaire Source: Evidence Review Group report page 46; manufacturer's submission page 244	

Evidence Review Group comments

6.12 The ERG noted that the manufacturer adapted an economic model previously used in NICE technology appraisals of cancer drugs; that is, a simple three-state model that includes progression-free survival, progressed disease and death health states. Effectiveness data for progression-free survival were taken directly from the probabilities observed in the BRIM3 study for the first 38 weeks and 30 weeks for vemurafenib and dacarbazine respectively, with exponential tails fitted thereafter. Modelling of overall survival is complex and is based on three sources: the BRIM3 study (up to 10–12 months), Robert et al (2011) data and SEER registry data.

6.13 The ERG considered that the manufacturer's modelling of overall survival was overly elaborate and involved a number of

assumptions. The ERG was particularly concerned about the assumption that survival gains continued to accrue after vemurafenib treatment was discontinued. The ERG further suggested that the manufacturer's modelling approach lacked a coherent underlying and compelling logic connecting the natural history of the disease. The ERG disagreed with the following assumptions presented by the manufacturer:

- A hazard ratio estimated from the BRIM3 data can be applied to extend the treatment effect of vemurafenib to 14 months.
- Results from a small sample of an arm of the Robert et al (2011) trial can provide reliable estimates for modelling the experience of both patients receiving dacarbazine and those receiving vemurafenib beyond 14 months of survival to 45 months.
- That long-term survival beyond 45 months can be adequately represented by a single mortality risk parameter calibrated to reconcile Robert et al (2011) trial data with a single value from the SEER database analysis at 10 years (the ERG considered that in doing this the manufacturer ignored the SEER hazard profile, which was based on the experience of over 1000 patients).

6.14 The ERG considered the manufacturer's approach to modelling 'progressive disease' as a single, absorbing health state may not be appropriate because skin lesions can spontaneously improve.

6.15 The ERG also noted that the cost of supporting BRAF V600 testing was not considered in the manufacturer's model, and suggested that, if considered, it would increase the ICER per QALY gained for vemurafenib compared with dacarbazine.

6.16 The ERG identified and corrected errors in the manufacturer's approach to discounting costs and outcomes (table 8). The

manufacturer discounted outcomes and costs weekly using fractions calculated based on the number of weeks in a year. The ERG was of the opinion that discounting should be applied annually, and found the revised ICER to be £484 lower per QALY gained than the manufacturer's base-case ICER.

6.17 The ERG re-estimated costs of therapy for dacarbazine based on distributions for body weight and body surface area found in a cohort of UK patients, rather than using the average reported in the BRIM3 trial (mean body-surface area in BRIM3 was 1.9141m^2). This led to a decrease in drug cost for dacarbazine, and an increase of £22 per QALY gained per patient compared with the manufacturer's base-case ICER (table 10). Assuming that dacarbazine would be administered as an oncology day case (£207 per session) led to a reduction of £218 per patient treated with dacarbazine and an increase in the base-case ICER of £380 per QALY gained.

6.18 The ERG sought clinical advice on the long-term monitoring costs (that is, a computed tomography [CT] scan and outpatient visits to an oncologist) for both vemurafenib and dacarbazine, and found that a programme of three to four times per year for 2 years (interval 1), reducing to twice a year for 2 years (interval 2), and then finally once a year (interval 3) thereafter was more likely than the manufacturer's estimate of £378 per month, which was based on an estimate found in the ongoing NICE technology appraisal 'Ipilimumab for previously treated unresectable stage III or IV malignant melanoma' (publication date to be confirmed). Taken together with GP consultations (4, 3 and 2 times a year for intervals 1, 2 and 3), the new annual costs estimated by the ERG were £1089 (interval 1), £645 (interval 2) and £339 (interval 3). This led

to a reduction in incremental cost of £520 and a reduction in the manufacturer's base case of £907 per QALY gained (table 10).

6.19 The ERG noted that almost 50% of adverse events were labelled as grade 3 or higher, and therefore it felt that a disutility should be have been applied to adverse events that led to a dose reduction. The ERG noted that the progression-free survival utility benefit applied by the manufacturer to vemurafenib may be optimistic because more than twice the number of patients on vemurafenib had their dose reduced or interrupted compared with patients receiving dacarbazine.

6.20 The ERG highlighted that the utility of 0.59 associated with long-term survival was likely to be an underestimate, and noted that if it was assumed that a utility of 0.767 was applied for patients with overall survival greater than 5 years (equivalent to utility for those with progression-free survival stable disease), this led to a reduction of £11,603 in the manufacturer's base-case ICER (reduced to £82,664 per QALY gained).

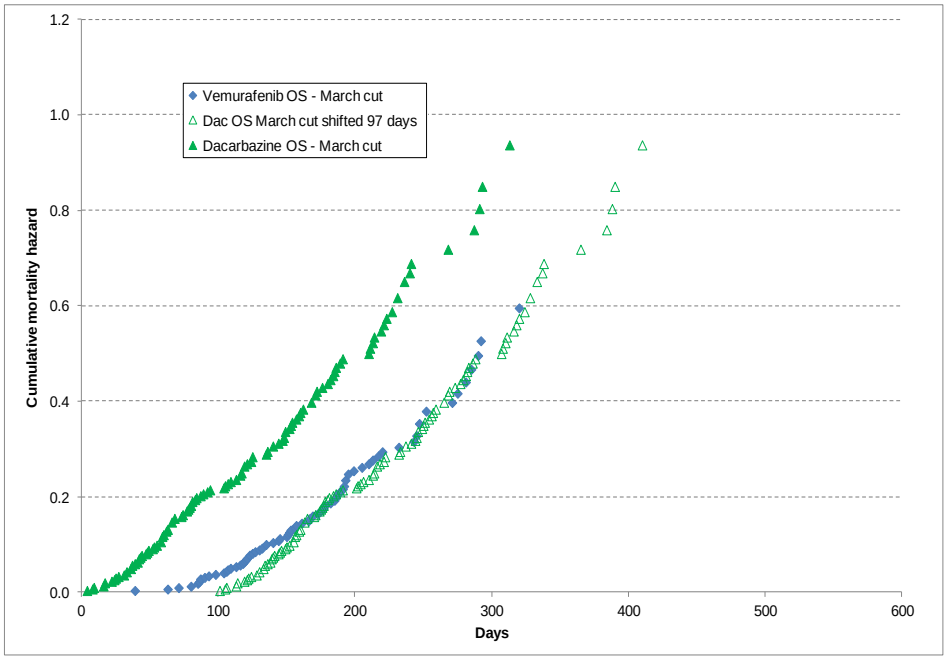
ERG exploratory analyses

6.21 The ERG explored an alternative approach to modelling overall survival. Based on the ERG's examination of the Kaplan-Meier overall survival plots from the BRIM3 trial, the ERG proposed that vemurafenib is very effective at suppressing disease progression leading to death in the early phase but, after a short period, this effect ceases and patients revert to the pattern of mortality risk seen in the dacarbazine arm.

6.22 The ERG tested this hypothesis by shifting the dacarbazine hazard plot forward in time until it matches, as far as possible, the vemurafenib trend (excluding the initial time period when both drugs are coming into full effectiveness before the long-term trend

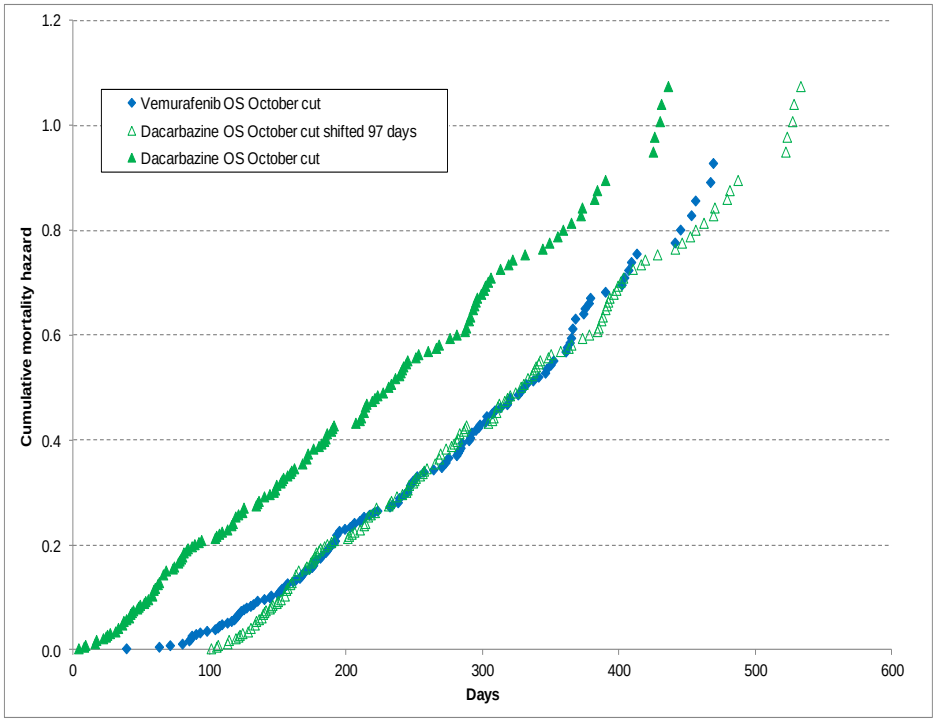
becoming established). This was tested on both the March 2011 and October 2011 data cut-offs and is displayed in figures 5 and 6.

Figure 5 Effect of shifting dacarbazine cumulative hazard plot forward 97 days (BRIM3 March 2011 data cut-off)



Source: Evidence Review Group report page 52

Figure 6 Effect of shifting dacarbazine cumulative hazard plot forward 97 days (BRIM3 October 2011 data cut-off)



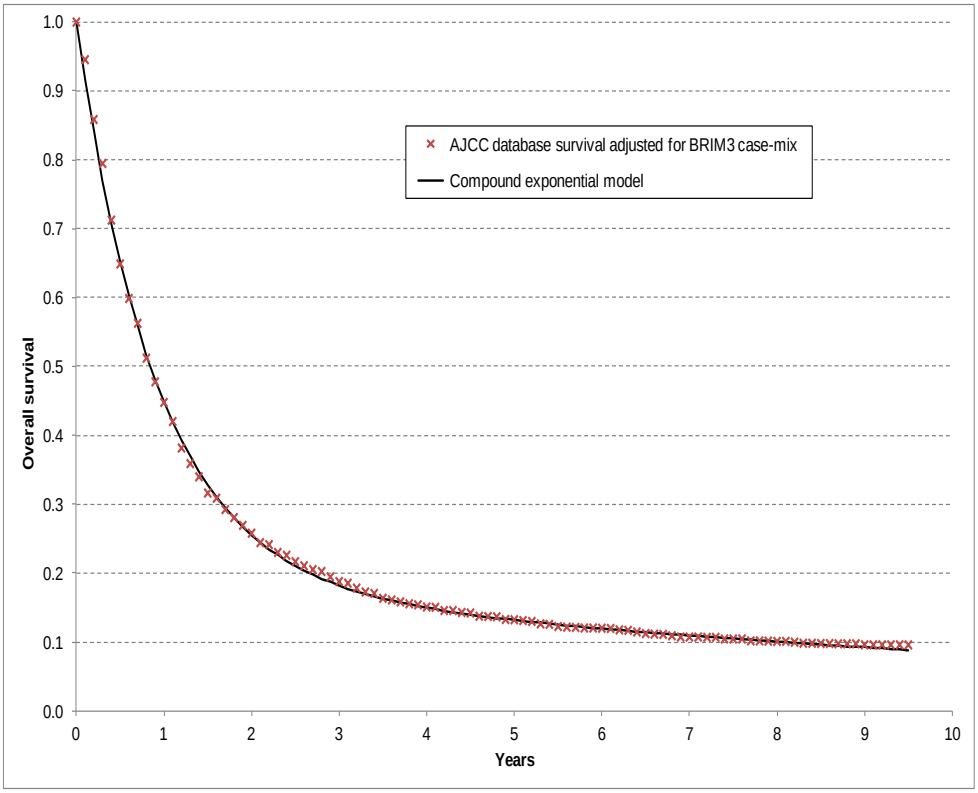
Source: Evidence Review Group report page 52

6.23 The ERG estimated that vemurafenib is effective at suppressing mortality for a limited period (that is, on average 97 days) after which it was assumed that it no longer provides any survival benefit compared with dacarbazine. The ERG noted that a limited window of effectiveness is supported by the observation that resistance is common with all new tyrosine kinase inhibitor drugs, reflecting the fact that cancer cells use multiple signalling pathways.

6.24 The ERG developed an alternative overall survival model considering the long-term prognosis of patients with malignant melanoma. The ERG noted that there appear to be two distinct populations of patients with malignant melanoma: the majority who have a poor prognosis with most dying within 12 months; and a small group who appear to have good prognosis and can survive for 10 years or more.

6.25 To address this, the ERG explored the simplest survival model that assumes two subgroups of patients split in an unknown ratio with each subgroup governed by a separate long-term mortality risk (equivalent to an exponential function). The ERG relied on a study by Balch et al (2009) that formed the final 2009 American Joint Committee on Cancer (AJCC) melanoma staging and classification system, and constructed a case-mix adjusted survival curve based on the proportions of patients in the BRIM3 trial (15.9% M0/M1a [no detectable evidence of distant metastases and metastases to skin, subcutaneous, or distant lymph nodes], 18.3% M1b [metastases to lung] and 65.4% M1c [metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH]). The ERG's compound survival model and the BRIM3 case-mix adjusted AJCC survival curve are shown in figure 7.

Figure 7 Compound exponential survival model (two subgroups) fitted to 2009 American Joint Committee on Cancer malignant melanoma data case mix adjusted to match the BRIM3 population



Source: Evidence Review Group report page 54

6.26 The fitted model results show 80.6% of patients having a mean survival of 11 months (0.91 years) and 19.4% of patents benefiting from an expected mean survival of over 12 years (145 months).

Table 10 Revised base-case cost-effectiveness analysis, incorporating corrections and amendments identified by the ERG

	Total				ICER
	Dacarbazine		Vemurafenib		
	Costs	QALYs	Costs	QALYs	
Manufacturer's base-case analysis	[redacted]	[redacted]	[redacted]	[redacted]	**£94,267**
Correct discounting logic	[redacted]	[redacted]	[redacted]	[redacted]	£93,783
Amend dacarbazine administration costs	[redacted]	[redacted]	[redacted]	[redacted]	£94,646
Amend post-progression utility value	[redacted]	[redacted]	[redacted]	[redacted]	£82,664
ERG estimate of dacarbazine costs	[redacted]	[redacted]	[redacted]	[redacted]	£94,289
Amend long-term monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	£89,745
ERG overall survival model	[redacted]	[redacted]	[redacted]	[redacted]	£230,175
Revised base case analysis with all ERG changes	[redacted]	[redacted]	[redacted]	[redacted]	**£224,704**

ERG, Evidence Review Group; QALY, quality-adjusted life year
Source: Evidence Review Group report page 56

6.27 Taking into consideration the ERG's approach to modelling overall survival (but not correcting for any other changes), the revised estimate for the manufacturer's base-case ICER for vemurafenib compared with dacarbazine is £230,175 per QALY gained (table 10). Taking into consideration all of the ERG's corrections (table 10) and the different overall survival modelling approach, the revised estimate for the base-case ICER vemurafenib compared with dacarbazine is £224,704 per QALY gained.

ERG's additional analyses

6.28 The ERG asked the manufacturer for results of an analysis designed to compare the outcomes in the BRIM3 trial of patients continuing treatment with vemurafenib until disease progression or death with those stopping treatment before disease progression or death. The ERG felt that vemurafenib may have only a restricted survival benefit rather than an indefinite mortality advantage.

6.29 To test this hypothesis within the limitations of the BRIM3 trial data, the ERG considered it would be helpful to compare outcomes (progression-free survival and overall survival) for patients receiving any vemurafenib who either continued treatment until confirmed disease progression or death with those who discontinued treatment prematurely for any reason. If outcomes were worse for those discontinuing treatment early, this might suggest that the efficacy of vemurafenib continues across most, or all, of the period to disease progression, but if there was no difference in outcomes it may suggest that patient benefit no longer continues to accrue after an initial period on therapy. Figure 8 shows the results based on [redacted] who discontinued treatment prematurely; the Kaplan-Meier survival plots for the two groups do not reveal any significant differences in either case.

[redacted]

A. Progression-free survival

B. Overall survival

6.30 The ERG estimated that if a maximum of five prescriptions of vemurafenib were given, the estimated ERG's revised base case ICER would be reduced by 40% (table 11).

Table 11 Revised-base case cost-effectiveness analysis, incorporating corrections and amendments by the ERG related to days of treatment

	Manufacturer's base case		with ERG changes	
Maximum vemurafenib treatment period (days)	**Cost of vemurafenib and administration**	**ICER per QALY gained**	**Cost of vemurafenib and administration**	**ICER per QALY gained**
112	[redacted]	£55,205	[redacted]	£127,665
140	[redacted]	£62,045	[redacted]	£144,832
168	[redacted]	£67,500	[redacted]	£158,560
196	[redacted]	£72,432	[redacted]	£171,004
224	[redacted]	£75,982	[redacted]	£179,986
Unlimited (to progression)	[redacted]	**£94,267**	[redacted]	**£224,704**

ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Source: Evidence Review Group report page 59

6.31 The manufacturer raised concerns with the legitimacy of the ERG's analysis on informing post-progression mortality of vemurafenib. The manufacturer was concerned with imbalances in the baseline characteristics and imbalances in post-progression treatments received by the patients in BRIM3. The ERG recognised that these are important areas of concern but noted that there were no significant differences in baseline characteristics (and that numerical differences must be clearly shown to have a strong influence on outcomes to raise concerns), and that age and gender of patients were not stratification variables. For details of the ERG's responses to the manufacturer's concerns, please see pages 59–60 of the ERG report.

7 Equalities issues

7.1 No equality issues were identified during the scoping process or in the submissions received.

8 Innovation

8.1 The manufacturer did not provide an argument for innovation. However, consultees and clinical specialists noted that vemurafenib is a targeted agent that rapidly reduces tumour response, provides symptomatic relief and offers the convenience of an oral formulation.

9 Authors

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Appendix A: Supporting evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Liverpool Reviews and Implementation Group:

- Dickson R, Beale S, Bagust A et al. Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (April 2011).

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Roche Products

II Professional/specialist, patient/carer and other groups:

- Dr Patrick Cadigan on behalf of the Royal College of Physicians
- Dr Louise Fearfield, clinical specialist representing the British Association of Dermatologists
- Professor Martin Gore, clinical specialist
- Dr Paul Lorigan, clinical specialist
- Steve Chalk, patient expert
- Gillian Nuttall, on behalf of Factor 50

Related NICE guidance

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Ipilimumab for previously treated unresectable stage III or IV malignant melanoma (publication date to be confirmed).

- Ipilimumab in combination with dacarbazine for previously untreated unresectable stage III or IV malignant melanoma (publication date to be confirmed).