STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

This report was commissioned by the NIHR HTA Programme as project number 11/43/01

Completed 12 April, 2012

Contains confidential data

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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

Produced by: Liverpool Reviews and Implementation Group

Authors: Sophie Beale, Decision Analyst, LR*i*G, University of Liverpool
Michaela Blundell, Research Associate (Medical Statistics), LRiG, University of Liverpool
Adrian Bagust, Professor of Modelling in Health, LR*i*G, University of Liverpool
Chris Proudlove, Director, North West Medicines Information Centre, Pharmacy Practice Unit, Liverpool
Rumona Dickson, Director, LRiG, University of Liverpool

Correspondence to: Ms Rumona Dickson, Director, LR*i*G , University of Liverpool, Room 2.12, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 12 April, 21012

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 11/43/01

Declared competing interests of the authors:
None

Acknowledgements:
Thanks to Dr. Ernie Marshall and Dr. Ruth Plummer who provided comments on the clinical aspects of the report, Mr James Mahon who provided comments on economic aspects of the draft report, Dr. Yenal Dundar for conducting the literature searches and Dr. Angela Boland for checking the document.

Rider on responsibility for report:
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Dickson R, Bagust A, Beale S, Blundell M and Proudlove C. 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.

Contributions of authors

Rumona Dickson	Project lead, drafted clinical results section and supervised production of the final report
Adrian Bagust	Critical appraisal of the economic model
Sophie Beale	Critical appraisal of the economic model
Michaela Blundell	Critical appraisal of the clinical statistical approach
Chris Proudlove	Critical appraisal of the manufacturer's submission

All authors read and commented on draft versions of the ERG report.

Table of contents

Abbreviations

AE(s)	adverse event(s)
BORR	best overall response rate
BSA	body surface area
BSC	best supportive care
CI	confidence interval
DSMB	Data safety monitoring board
ECOG	Eastern Co-operative Oncology Group
EMA	European Medicines Agency
ERG	Evidence Review Group
FACT-M	A validated and internationally recognised tool to measure quality of life in melanoma clinical trials
FDA	Food and Drug Administration
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost-effectiveness ratio
ITT	Intention-to-treat
LDH	lactate dehydrogenase
LYG	life year gained
MS	manufacturer's submission
NICE	National Institute for Health and Clinical Excellence
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PP	per protocol
PPS	post-progression survival
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TKI	threonine kinase inhibitor

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE from Roche in support of the use of vemurafenib (Zelboraf®) for treatment of locally advanced or metastatic BRAF V600 mutation positive malignant melanoma. Vemurafenib is an oral medication given continuously until disease progression and is compared with conventional IV chemotherapy (typically dacarbazine). It requires genetic testing to establish mutation status before treatment

The manufacturer's submission (MS) outlines the use of single agent vemurafenib for two groups of patients: (i) previously untreated patients and (ii) patients who have previously received treatment. The manufacturer is seeking approval only for the former group of patients.

Vemurafenib has a marketing authorisation in Europe. It is a novel protein-kinase inhibitor that is approved for use in the treatment of patients with BRAF V600 mutations of metastatic or unresectable melanoma regardless of whether they have had previous treatment.. The approval documentation acknowledges that the risk of secondary neoplasms (squamous cell carcinoma of the skin) is important and the EMA has accepted the manufacturer's pharmacovigilance plan.

1.2 Critique of the decision problem in the manufacturer's submission

The manufacturer has presented a case for approval of vemurafenib in a more limited population of patients than listed in the scope – that is, patients who are treatment näive. This decision was taken due to the lack prospective randomised data in the patients who have previously received treatment. This has the effect of also limiting the comparator to dacarbazine.

1.3 Summary of clinical effectiveness evidence submitted by the manufacturer

The evidence presented in the MS is from a well designed multi-national randomised controlled trial (RCT – BRIM 3) that demonstrated improved overall survival (OS) and progression free survival (PFS) in patients receiving vemurafenib compared to those that received dacarbazine. The median OS benefit for vemurafenib compared to dacarbazine was 13.2 and 9.6 months respectively, with a hazard ratio (HR) of 0.62 (95% CI 0.49 to 0.77). Median PFS was 5.32 months compared to 1.61 month with a HR 0.26 (95% CI 0.20 to 0.33).

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The manufacturer carried out a literature search for randomised evidence related to the efficacy of vemurafenib. Three manufacturer sponsored studies were identified, only one of which was a RCT. The earliest study was a dose ranging trial in a variety of cancers, the second was a single-armed trial in previously treated patients with malignant melanoma that were BRAF V600 mutation positive. Data from this second trial was not considered robust by the manufacturer and they appropriately limited their submission to the treatment of patients who had not previously received a systemic treatment.

The data presented from the RCT (BRIM 3) demonstrate a statistically significant difference for both OS and PFS in favour of vemurafenib over dacarbazine in patients with locally advanced or metastatic BRAF V600 mutation positive malignant melanoma who have not received previous treatment. The trial that provided this data was well designed, however based on requests from the approval authority (FDA), changes were made to the statistical analysis plan (SAP) that resulted in the single primary outcome of OS being amended to joint primary outcomes of OS and PF. As a consequence of the positive interim analysis in December 2011, patients in the comparator arm were allowed to cross over to the vemurafenib arm of the trial.

1.5 Summary of cost effectiveness submitted evidence by the manufacturer

In the absence of any relevant published economic evaluations comparing vemurafenib with dacarbazine for the treatment of local advanced or metastatic BRAF V600 mutation positive malignant melanoma, the manufacturer developed a *de novo* economic model. The model, constructed in Microsoft Excel, is composed of three patient health states (PFS, progressive disease (PD) and death). The model population is based on the patients enrolled in the BRIM 3 trial. Effectiveness data for PFS have been taken directly from probabilities observed in the BRIM 3 trial for the first 38 and 30 weeks for vemurafenib and dacarbazine respectively, with exponential tails fitted thereafter. The modelling of OS is more complex. It is based on data from three sources; BRIM 3, Robert et al and SEER registry data, and encompasses both hazard ratios and a number of exponential functions. The economic evaluation adopts a time horizon of 30 years, and the perspective is that of the UK NHS. Resource use, costs and utilities have been estimated based on information from trial data and published sources.

The manufacturer's reported base case incremental cost-effectiveness ratio (ICER) is £94,267 per quality adjusted life year (QALY) gained. The manufacturer showed this ICER to be generally robust when subjected to a range of deterministic sensitivity analyses, with reported ICERs ranging from £70,358 to £110,535 per QALY gained. The manufacturer's probabilistic sensitivity analyses (PSA)

showed that vemurafenib would be considered cost effective in 0% of simulations up to a willingness to pay threshold of £85,000 per QALY gained.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

Overall, the ERG found the manufacturer's model to be clearly set out with adequate labelling of tables and parameters. The main area that gave cause for concern was the modelling of OS. The method of extrapolation used by the manufacturer to project the limited BRIM 3 data available (up to 10 – 12 months) out to 30 years is extremely elaborate, employing six time phases and multiple assumptions, each of which is vulnerable to challenge. The approach used lacks a coherent underlying logic connecting the natural history of the disease, the mode of action of the interventions and the accumulated experience of clinicians and patients.

The ERG has also identified a number of other areas where corrections and/or adjustments to the economic model are required. These relate to discounting; estimation of dacarbazine costs; dacarbazine administration cost; long-term monitoring costs; and utility associated with patients who survive for more than 5 years.

1.6.1 Strengths

Clinical data reported in the submission comes from a well designed multi-centre, multi-national RCT.

1.6.2 Weaknesses and areas of uncertainty

The main weakness with the economic model relates to the modelling of OS. The ERG has concerns that the current approach is overly complex and lacks a compelling underlying logic. Moreover, the approach includes the assumption that vemurafenib continues to yield survival gains after the treatment is discontinued. The ERG has found that such a continued survival gain is not supported by BRIM 3 trial data.

A number of other, relatively minor, issues relating to the model are discounting logic; estimation of dacarbazine costs; dacarbazine administration cost; long-term monitoring costs; and utility associated with patients who survive for more than 5 years were identified.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made five relatively minor alterations/corrections to the manufacturer's model, namely:

- Correcting discounting logic

- Recalculating dacarbazine drug costs based on the distribution of patient body weight and body surface area (BSA) of a UK specific cohort of patients, rather than a simple average based on trial data

- Amending the dacarbazine administration cost for treatment in a day case unit

- Adjusting long-term monitoring costs based on the clinical advice that, for patients with long-term survival, monitoring will not be continued indefinitely

- Adjusting the post-progression survival (PPS) utility value based on the assumption that all patients with OS greater than 5 years will have a long-term utility value equivalent to PFS (stable disease) rather than the much lower utility value associated with PD.

The ERG also employed the use of an alternative interpretation of the BRIM 3 OS data and a different survival model. Combining all of the ERG's changes results in an ICER of £226,144 per QALY gained.

1.7.1 Further analyses

The ERG undertook two exploratory analyses. The first investigated whether there were any differences in outcomes between those patients receiving any vemurafenib who continued treatment until confirmed disease progression or death, and those patients who discontinued vemurafenib treatment prematurely for any reason. No difference in outcomes was identified (though the number of deaths in the OS analysis is too small to draw strong conclusions), and this suggests that patient benefit may no longer continue to accrue after an initial period on therapy. If it proves possible to determine a maximum effective duration of vemurafenib treatment in this patient population then such a finding would have an important bearing on the assessment of cost effectiveness.

The second exploratory analysis investigated whether there is any evidence from BRIM 3 supporting the notion that vemurafenib continues to yield survival gains after the treatment is discontinued. A tentative conclusion from this analysis is that the available evidence provides no grounds for expecting vemurafenib therapy to be associated with any better PPS than dacarbazine. Therefore, the ERG consider that any projective modelling which results in extended PPS due to vemurafenib is not supported by the BRIM 3 trial results.

The manufacturer raised a number of arguments against the legitimacy of the second analysis. Whilst the ERG recognises the manufacturer's concerns, which relate to imbalances between the subgroups, the ERG considers that the issues raised also apply to the BRIM 3 OS patient data and projections obtained from it.

1.7.2 Conclusion

Trial data provided in the MS demonstrates the efficacy of vemurafenib in terms of OS and PFS in treatment naive patients with locally advanced or metastatic BRAF V600 mutation positive malignant

melanoma. The short term nature of the results and the heterogeneity of the patient population impose substantial uncertainty on any projection of the long term benefits. The cost of the intervention and the extended duration of treatment for some patients means that, within all considered situations, the case presented by the manufacturer produces an incremental cost per QALY gained greater than £90,000. Additional analysis carried out by the ERG has identified that given the uncertainty related to the OS benefit the figure could be much higher.

2 BACKGROUND

2.1 Critique of MS description of underlying health problem

The manufacturer's submission[1] (MS) (Summary and Section 2), appropriately presents the key issues related to the underlying health problem, including epidemiology, diagnosis and prognosis. A summary of these sections is presented in Box 1.

Box 1: Epidemiology and prognosis

Aetiology and Epidemiology

Melanoma is a malignancy of melanocytes, which are cells responsible for the production of the pigment melanin. Melanoma accounts for less than 5% of all skin cancers; however, it causes 90% of all skin cancer-related deaths worldwide.

Metastatic melanoma is one of the most aggressive cancers; however, relatively few patients (less than 2,000 annually in the UK) progress to the metastatic stage since most melanomas are diagnosed early and cured by surgery.

Diagnosis and Prognosis

Approximately 90% of melanomas are diagnosed as primary tumours without any evidence of metastasis. These are treated by surgical excision and the tumour-specific 10-year-survival for such tumours is 75 to 85%. Around 10% of patients have metastatic disease at diagnosis or relapse with metastatic spread after treatment for apparently localised disease. Survival for patients with metastatic disease is very poor with 5 year survival of 7-20% for stage IV disease.[2]

Median prognosis in inoperable melanoma is extremely poor (median overall survival with stage IV melanoma is only around 6 months) and over 80% of patients diagnosed with advanced melanoma will have died less than 2 years after diagnosis.[3] Patients with uncontrolled (i.e. progressive) metastatic disease are generally very symptomatic with a consequently low quality of life.

The ERG report submitted for a previous NICE appraisal of ipilimumab in a similar population[4] highlighted out that malignant melanoma is the least common but also the most serious type of skin cancer. In 2008 there were 11,767 new cases diagnosed in the UK, and 2067 deaths.[5] UK incidence rates have increased more rapidly over the past 25 years than any of the top ten cancers in males and females, and malignant melanoma was the sixth most common cancer diagnosed in females in 2008.[5] The mortality rate in people aged 65 years and older has almost tripled since 1979 from four deaths per 100,000 to 11.4 deaths per 100,000 in 2008.[5]

Issues related to prognosis however are more difficult to address. Balch et al[6] provide an excellent overview of staging and prognosis of melanoma related to the stage of disease at the time of diagnosis. It is clear that patients with more advanced disease have a much poorer prognosis.

2.2 Critique of MS overview of current service provision

The MS appropriately outlines the current service provision for patients with malignant melanoma (Box 2) including a discussion related to BRAF mutation screening. The MS highlights that BRAF testing is currently not a part of the patient care pathway in the National Health Service (NHS) for patients with unresectable melanoma and that approval of vemurafenib by NICE will require BRAF testing to be carried out on all these patients.

Box 2: Current treatment and mutation screening

Current treatment options

There is a paucity of effective treatments for inoperable melanoma.

Currently the majority of patients receive dacarbazine (a chemotherapy) as a first-line agent. Dacarbazine is intravenously (IV) administered every 21 days. Following relatively rapid progression on first-line dacarbazine (median PFS in BRIM 3 = 1.6 months) patients are faced with the choice of participating in a clinical trial, receiving best supportive care alone until death or (if available in their local region) receiving ipilimumab (the only second line treatment with benefit demonstrated in a randomised controlled trial) via the English Cancer Drug Fund.

BRAF Mutations

Following implication of mutated variations of BRAF in the proliferation of melanoma, vemurafenib was developed in order to selectively inhibit these and thereby prevent downstream signalling of the MAPK pathway, which drives tumour growth. Approximately 50% of melanoma patients have tumours which harbour BRAF V600 mutations.[7]

The manufacturer references an Australian study[7] which states that approximately 50% of patients with malignant melanoma will test positive for BRAF mutation. The ERG notes that there may be variation in this figure. BRAF V600 positive screening rates from available trials are presented in Table 1.

Table 1 BRAF V600 mutation incidence

Study	No. screened	No. +ve (%)	No. enrolled (%)
Long[7]	207	97 (47)	N/A
BRIM 2[8]	328	184 (56)	132 (40)
BRIM 3[9]	2107	Not reported*	675 (32)

*exact figures not provided -report states that the most common reason for screening failure was a negative BRAF test

In BRIM 2[8] and BRIM 3[9] the most commonly reported reason for patients not being included in the study was that their tumours were BRAF V600 mutation negative. However, BRIM 2[8] also reports that 23 patients failed due to central nervous system metastases but they do not indicate what proportion of these patients tested BRAF V600 mutation positive. It is therefore somewhat unclear what the exact proportion of patients who are tested will be eligible for treatment. Based on the assumption that 50% of patients with malignant melanoma (that is Stage IIIc/IV) are BRAF V600

positive of whom 85% will be eligible for treatment the manufacturer estimates that that 850 patients will be eligible for treatment with vemurafenib each year (MS pg 27).

NICE has produced clinical guidelines for the management of patients with skin cancer,[10] primarily focused on low risk basal cell carcinomas. Currently there is no NICE guidance for treatment of patients with metastatic melanoma. NICE reviewed the use of ipilimumab for the second-line treatment of this disease, and the outcome of that appraisal is due to be made publically available on 18 April, 2012.[11]

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

The MS presents the decision problem issued by NICE,[2] and their rationale for any deviation from this in the MS. The details are outlined Table 2.

Table 2 Decision problem as addressed in MS

	NICE Final scope	**Decision problem addressed in MS**	**Rationale if different from the scope**
Population	People with unresectable locally advanced or metastatic BRAFV600 mutation positive malignant melanoma	As per scope	N/A
Intervention	Vemurafenib	As per scope.	N/A
Comparator(s)	For people with previously untreated malignant melanoma: dacarbazine For people with previously treated malignant melanoma: ipilimumab (subject to ongoing NICE appraisal) Best supportive care	As per scope for previously untreated melanoma. See 'rationale if different from scope' for discussion on previously treated patients	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
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	N/A
Economic analysis	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	N/A

3.1 Population

The population as outlined in the scope and the key submitted trial (BRIM 3[9]) are not the same. The scope includes all patients with unresectable locally advanced or metastatic BRAF V600 mutation positive disease. The submission and evidence relate only to patients who have not previously received treatment. See section 3.3 below where this is discussed in more detail.

3.2 Intervention

The MS outlines that 'Vemurafenib is an oral tyrosine kinase inhibitor (TKI) of the BRAF serine-threonine kinase' and that 'following implication of mutated variations of BRAF in the proliferation of melanoma, vemurafenib was developed in order to selectively inhibit these and thereby prevent downstream signally of the MAPK pathway, which drives tumour growth' (MS pg 9).

The drug is used as a monotherapy at a dose of 8 x 240 mg tablets per day until disease progression or unacceptable toxicity. Down-dosing may be an appropriate response to toxicity. One week's supply of the treatment has a list price of £1750 with an approximate drug cost of [redacted] per patient.

Vemurafenib received market authorisation from the European Medicines Agency (EMA) in February, 2012.[12] It is approved for use in the treatment of patients with BRAF V600 mutations of metastatic or unresectable melanoma. The approval acknowledges that the risk of secondary neoplasm (squamous cell carcinoma of the skin) is low and the EMA has accepted the manufacturer's pharmacovigilance programme.

3.3 Comparators

As noted above, the MS submits a data only for patients who have not previously received treatment. The original scope outlined that the treatment should be considered in both the first- and second-line treatment settings. The MS outlines the lack of robust randomised controlled trial (RCT) data related to the use of the drug in the second-line setting and therefore is seeking NICE approval only for first-line treatment of patients with BRAF V600 mutation positive malignant melanoma.

Given the lack of available therapies for these patients, the manufacturer has appropriately followed the decision problem and compared their treatment to dacarbazine in the first-line setting.

3.4 Outcomes

Direct data related to the first four outcomes stated in the scope (overall survival (OS), progression-free survival (PFS), response rate reported as best overall response (BORR) and adverse event (AE)) are described in the MS. Health related quality of life (HRQoL) data were collected using the FACT-M questionnaire during the BRIM 3[9] trial, however these data have not been presented. Reasons for this cited in the MS are linked to poor completion rates (especially after the interim analysis) and that

the FACT-M questionnaire is not preference based and therefore does not conform to the NICE base case.

A variety of protocol changes requested by the Food and Drug Administration (FDA) resulted in the primary outcome of the BRIM 3[9] trial being changed from OS to a joint primary outcome of OS and PFS. The MS reports that the trial has met its primary outcome but that further reporting of long term outcomes will be forthcoming. Further reporting of OS is due to be provided to the EMA in May 2012.

3.5 Other relevant factors

In order to receive treatment with vemurafenib a BRAF V600 mutation test is required. Testing of various BRAF identification systems was undertaken in the BRIM 3 clinical study. These were done to meet a secondary trial objective which was to provide validation for the cobas® 4800 BRAF V600 mutation test that was used in the trial.

BRAF V600 mutation testing is not routinely available in the UK NHS. The manufacturer has offered assistance to clinicians wishing to use vemurafenib by providing such testing in three UK collaborative laboratories (Institute of Cancer Research, Surrey; Queen Elizabeth Hospital, Birmingham; and Saint Mary's Hospital, Manchester). Clinical input to this single technology appraisal (STA) identified that there is considerable cost to the NHS prior to this testing (e.g. identifying tumour blocks, preparing them and sending them to the laboratories). This is becoming a growing issue, not just in the case of malignant melanoma, within many pathology laboratories with the increase in the number of new targeted drugs.

No issues related to equity were identified in the MS or by the ERG.

4 CLINICAL EFFECTIVENESS

The manufacturer has provided details of three studies; BRIM 1,[13] BRIM 2,[8] and BRIM 3.[9] Support for the submission is provided in the main from the BRIM 3 trial.[9]

Table 3 Key clinical information in the MS

Key information	Page(s) in the MS
Description of the technology	9
Context	25-31
Statement of decision problem	33-36
Literature search main	37 and 91-92
Study selection	38 and 93
Clinical effectiveness evidence key trial	43-88

4.1 Critique of the methods of the clinical reviews

Two separate systematic literature searches were carried out to identify relevant studies of vemurafenib used as monotherapy in the treatment of malignant melanoma. The first was designed to identify RCTs and the second to identify non-randomised studies. Appropriate search strategies and inclusion criteria were utilised. All identified studies had been sponsored by the manufacturer.

4.1.1 Identified studies

A total of three studies[8,9,13] that examined the use of vemurafenib as monotherapy were identified by the searches conducted by the manufacturer. Details of these studies are reported in the MS and are presented in Table 4. The only direct evidence used in the MS for this STA comes from the BRIM 3[9] trial. Therefore data from the other two studies are not considered in any depth by the ERG. Reports of all three trials have been published.

Table 4 Identified vemurafenib studies

	BRIM 3[9]	BRIM 2[8]	BRIM 1[13]
Design	RCT n=675	Phase II open label – single arm n=132	Phase 1 dose ranging n=55
Location	International multi-centred	USA and Australia	USA and Australia
Patient inclusion criteria	Previously **untreated** BRAF mutation positive melanoma patients (Stage IIIC or IV)	Previously **treated** BRAF mutation positive melanoma patients	Previously **treated** BRAF mutation positive patients with solid tumours (advanced melanoma and metastatic colorectal)
Interventions and comparators	Vemurafenib 960 mg orally BID Dacarbazine 1000mg/m^2 IV every 3 weeks	Vemurafenib 960 mg orally BID n/a	Vemurafenib – varied dosage orally BID n/a
Primary outcome	OS PFS	ORR	Safety/Adverse events Pharmacodynamic activity in tumour tissue
Secondary outcomes	BORR – complete or partial as measured by RECIST Duration of response Time to response Tolerability and safety	OS	
Timeframe	January to December 2010 Follow-up continues	2009-2011	2006-09
Patient inclusion criteria	Male or female>18 Histologically confirmed metastatic melanoma (Stage IIIc or IV) Treatment naive BRAF V600-positive mutation ECOG status 0-1 Life expectancy > 3 months Measureable disease by RECIST criteria Recovered from recent injury Excision of any squamous cell carcinoma lesions Adequate haematological , renal and liver function	Male or female > 18 Histologically proven stage IV melanoma BRAF V600-positive mutation Progressive disease following at least one prior systemic treatment ECOG status 0-1 Brain metastasis controlled for at least 3 months No other invasive cancer in last 5 years Adequate haematological, renal and hepatic function	Male or female > 18 Solid tumours Histologically refractory to standard care or no care available ECOG status 0-1 Life expectancy of > 3 months Absence of known progressing or unstable brain metastases Adequate haematological, renal and hepatic function
Trial sponsorship	Hoffmann-La Roche	Hoffmann-La Roche	Plexxikon and Roche Pharmaceuticals

RCT=randomised controlled trial; OS=overall survival; PFS=progression free survival; ORR=overall response rate; BORR=best overall response rate;ECOG European Co-operative Oncology Group

4.1.2 BRIM 3[9] trial characteristics

As noted above, BRIM 3[9] is an international multi-centred RCT that included patients previously untreated for BRAF V600 mutation positive malignant melanoma. Vemurafenib (960 mg twice a day) until disease progression or toxicity was compared with dacarbazine (1000 mg/m^2) every 3 weeks until disease progression or unacceptable toxicity. Patients were stratified by the American Joint Committee on Cancer Stage (IIIC, M1a, M1b or M1c), ECOG performance status (0 or 1), geographic region (North America, Western Europe, Australia, New Zealand or other) and serum lactate dehydrogenase level (LDH) - normal or elevated.

Patient characteristics by treatment group are presented in Table 5.

Table 5 BRIM 3[9] Patient baseline characteristics

	Vemurafenib	Dacarbazine
N=675	n=337	n= 338
Stratification factors no (%)		
Geographic region		
Australia or New Zealand	39(12)	38 (11)
North America	86 (26)	86 (25)
Western Europe	205 (61)	203 (60)
Other	7 (2)	11 (3)
ECOG status		
O	229 (68)	230 (68)
1	108 (32)	108 (32)
Extent of metastatic melanoma		
M1c	221 (66)	220 (65)
M1b	62 (18)	65 (19)
M1a	34 (10)	40 (12)
Unresectable IIIC	20 (6)	13 (4)
Lactate dehydrogenase (LDH)		
≤ Upper limit of normal range	142 (42)	142 (42)
>Upper limit of normal range	195 (58)	196 (58)
Other factors		
Median age (range)	56 (21-86)	52 (17-86)
Males	200 (59)	181 (54)
Race – white	333 (99)	338 (100)

Clinical opinion to the ERG indicated that although the patients in the BRIM 3[9] trial may be younger than those typically seen in clinical practice they are the patients who would be considered for aggressive treatment of their disease which tends to be a more aggressive form. Consistent with other trials, the patients in the population studied are also somewhat fitter than the patients who would be assessed for treatment in the UK clinical setting; as has been noted in earlier appraisals it is not known

how patients with a poorer performance status respond to the treatment. In addition, patients with brain metastases were excluded from the trial.

4.1.3 BRIM 3[9] quality and validity assessment

The quality assessment of the BRIM 3[9] trial is presented on pages 70-76 of the MS. The assessment demonstrates that it was generally a well designed international, multi-centre trial. There are however some areas of trial design that should be noted.

Although there was appropriate concealment of allocation and randomisation, the trial was not blinded. The MS appropriately presents a case that given the poor prognosis in these patients it would have been inappropriate to subject participants to unnecessary additional clinical visits and treatments. It is of interest to note that the trial was able to recruit its full original sample size in less than 12 months reflecting the lack of other viable treatments and the hope for a new and new active treatment.

Important changes to the study design and data analysis were required by the FDA regulatory system as the trial progressed. These included a change in the primary outcome (from OS to joint primary outcomes of OS and PFS) and the crossover of patients from the dacarbazine group. The effects of these changes are discussed in a later statistical analysis section of this report. The most recent data cut was in October 2011 and the data remain immature. Analysis of OS is due again at the end of May 2012 for review by the EMA.[14]

The randomisation process produced equivalent groups; however, 14% (48/338) of patients randomised to receive dacarbazine did not receive treatment. The most common reasons were withdrawal of consent or refusal of treatment (37/48). It is not known what impact this may have had on data analysis related to the intention to treat (ITT) and per protocol (PP) populations.

Data related to HRQoL were collected using the FACT-M questionnaire. However, the MS reports that completion rates were low following the reporting the results of the interim analysis. In addition, the MS points out (pg189) that the tool is not preference based and therefore does not conform to the NICE reference case.

4.1.4 BRIM 3[9] outcome selection

The BRIM 3[9] study outcome measures and their definitions are presented in Table 6.

Table 6 BRIM 3[9] Outcomes

Outcome	Definition and measure	Time of assessment
Co-primary outcomes		
Overall survival (OS)	Defined as the time from randomisation to death from any cause. For patients who were alive at the time of analysis data cut-off, OS time was censored at the last date the patient was known to be alive prior to the clinical cut-off date.	
Progression free survival (PFS)	Defined as the time from randomisation to the date of disease progression (based on tumour assessment date) or death from any cause, whichever occurred first. The death of a patient without a reported progression was considered as an event on the date of death. Patients who had neither progressed nor died were censored on the date of last evaluable tumour assessment prior to the clinical cut-off date.	Tumour assessments at baseline, at weeks 6 and 12 and every 9 weeks thereafter.
Secondary objectives		
Best overall response rate (BORR)	Defined as a complete response (CR) or partial response (PR) which was confirmed per RECIST version 1.1.	
Duration of response	Defined as the time from the date of the earliest qualifying response to the date of disease progression or death from any cause. For patients who were alive without progression following the qualifying response, duration of response was censored on the date of last evaluable tumour assessment before the data cut-off date.	
Time to response	Defined as the time from randomization to the date of the earliest qualifying response.	
Other outcomes		
Tolerability and safety	Adverse events reported	
Phamacokinetic profile of vemurafenib	Not reported in the MS	
Validation of cobas® 4800 BRAF V600 Mutation test	Not reported in the MS	
Health related quality of life (HRQoL)	FACT-M questionnaire - results not reported	Baseline, day 1 (pre-dose) of cycles 2, 3, 4, 6, 9 and 12, and within 28 days after documented progression.

4.1.5 Description and critique of the statistical approach

Blinding and concealment

The BRIM 3 trial[9] was an open-label study; investigators, patients and sponsor were all aware of treatment allocations after randomisation had taken place. One of the co-primary endpoints was PFS which is a subjective outcome and therefore the lack of blinding could lead to potential bias, especially as there was no independent review committee to reinforce the assessments made by investigators. The other co-primary endpoint, OS, is objective so the ERG has no concerns about any bias introduced by the lack of blinding for this outcome.

It is still important to have allocation concealment in an open-label study, whereby the investigators are not aware of the treatment that the patient will be assigned before randomisation takes place. This was achieved in the BRIM 3 study[9] by randomising patients centrally using an interactive voice response system. The ERG is satisfied that allocations were adequately concealed in this trial.

Randomisation

According to the statistical analysis plan (SAP),[15] patients were randomised (1:1) to receive treatments based on a minimisation algorithm using the following balancing factors:

- Geographic region (North America, Western Europe, Australia/New Zealand, others)
- ECOG performance status (0,1)
- Metastatic classification (unresectable stage IIIC, M1A, M1B, M1C)
- Serum lactate dehydrogenase (LDH) (normal, elevated)

Minimisation is a method of treatment allocation whereby the first patient is truly randomly allocated and then for subsequent patients, the treatment that minimises the imbalance on the selected factors (described above) between the groups at that time is identified. This allocation may then be used or a random element may be introduced so that although there is a heavy weighting (commonly 80%) towards the treatment that minimises the imbalance, there is still a chance that the patient may be allocated to the other treatment. The approach where a random element is incorporated is generally preferred. It is not clear whether the minimisation algorithm adopted by the manufacturer utilised a random element but the ERG is satisfied with the approach taken as it is stated in the CONSORT statement[16,17] that "in general, trials that use minimisation are considered to be methodologically equivalent to randomised trials, even when a random element is not incorporated" (pg 9).

Protocol and SAP amendments

The original primary endpoint of the study was OS, defined as the time from randomisation to death from any cause. The SAP[15] was revised in October 2010 on the basis of phase 1 and 2 efficacy and safety results and after consultation with the FDA.[18] Under the revised plan, there were two co-

primary endpoints: PFS, defined as the time from randomisation to the date of disease progression (based on tumour assessment date) or death from any cause, and OS, defined as before.

[redacted]

Populations and analyses

According to the SAP,[15] the primary analysis population for efficacy was the intention-to-treat (ITT) population defined as all randomised patients, whether or not the study treatment was received, analysed according to the treatment assigned at randomisation. It should be noted that full application of the ITT principle is only possible when complete outcome data are available for all randomised patients.[19] The ERG is concerned that the analyses conducted by the manufacturer were not strictly performed using an ITT population as evaluable populations did not include all randomised patients. Details relating to the numbers of patients used in the analyses are discussed later in this report.

All safety analyses were performed on the safety population, defined as all randomised patients who received any amount of study treatment (vemurafenib or dacarbazine) and had an on-study assessment, analysed according to the treatment received.

Populations defined for exploratory analyses include the non-BRAF V600E mutation positive and the per-protocol (PP) populations. The non-BRAF V600E population was defined as the subset of the ITT population whose mutation status was identified as positive for a BRAF V600 mutation other than V600E (i.e. V600K, V600D, or V600R). The PP population was defined as treated patients (safety population), excluding patients who violated any of the exclusion criteria below, and was analysed according to the treatment received.

- Histologically confirmed metastatic melanoma (surgically incurable and unresectable stage IIIC or stage IV as defined by the American Joint Committee on Cancer)
- Positive for BRAF V600E mutation by Roche CoDx test
- No prior systemic anti-cancer therapy for this disease
- ECOG performance status 0 or 1.

There was one interim analysis planned for OS, which was to be performed when approximately 98 deaths (50% of the planned 196 in the final analysis) had occurred. The Lan-DeMets alpha spending method of the Pocock type boundary was used to control the alpha level, and statistical significance for OS at the interim analysis was to be claimed if the log-rank p-value (two-sided) was ≤ 0.028. Under the assumptions that the efficacy stopping boundary for OS was not crossed at the time of interim analysis, and that 98 of the planned 196 deaths had been observed at the time of the interim analysis, then significance for OS at the overall two-sided 0.045 level would be achieved at the final analysis if the p-value ≤ 0.0247. It was planned that the final analysis for PFS would take place at the time of the interim analysis of OS.

The statistical methods used to analyse the efficacy outcomes in the trial are presented in Table 7. It was stated in the SAP[15] that both BORR (confirmed) and BORR (confirmation not required) would be evaluated as secondary outcomes. However, it was later decided to drop BORR (confirmation not required) as a secondary outcome as BORR (confirmed) is a more meaningful measure of clinical benefit.

Table 7 Efficacy analyses

Outcomes	Method of analysis
Overall survival, progression free survival	Comparison of the two treatment groups, made using an unstratified log-rank test (two-sided). Median OS/PFS times estimated using the Kaplan-Meier method, and the 95% confidence intervals calculated using the Brookmeyer and Crowley method. Hazard ratios for vemurafenib relative to dacarbazine and associated two-sided 95% CIs computed using the Cox proportional hazards model. In addition, Kaplan-Meier estimates of 6-month OS and PFS and associated 95% CIs provided.
Best overall response rate (BORR) – confirmed	If either of the co-primary endpoints met respective criteria for statistical significance, BORR evaluated for statistical significance at the 0.05 level (two-sided). BORR and associated 95% Clopper-Pearson CI calculated. Difference in BORR between treatment arms and associated 95% Hauck-Anderson CI calculated. BORR compared between treatment groups using a Chi-squared test with Schouten correction.
Duration of response	Estimated using Kaplan-Meier method, and 95% CI calculated using method of Brookmeyer and Crawley. No formal hypothesis testing.
Time to response	Summarised using descriptive statistics (median, 25% and 75% quartiles, minimum and maximum). No formal hypothesis testing.

Exploratory and subgroup analyses

Further analyses were also performed for exploratory purposes only; these were analyses of patient-reported outcomes (FACT-M and pain), physical symptom-improvement outcomes, efficacy outcomes in the non-BRAF mutation (e.g. V600E) positive population and efficacy outcomes in the

PP population. An additional analysis whereby outcomes would be analysed by dose intensity was also planned but this analysis was not performed. Analyses of the relationships between exposure and outcomes are summarised in the Clinical Pharmacology Summary.[20]

For both OS and PFS, sensitivity analyses in the form of a stratified analysis based on metastatic classification, LDH and ECOG performance status were planned along with the following additional censored analyses:

- OS censored for potential subsequent use of vemurafenib in the dacarbazine arm
- OS censored for subsequent anti-cancer therapy
- PFS censored for non-protocol anti-cancer therapy
- PFS censored to account for missing visits.

Several subgroup analyses were also planned to assess the potential impact of age (< 65 years vs ≥ 65 years and < 40 years vs 41-54 years vs 55-64 years vs 65-74 years vs ≥ 75years), race (non-white vs white), gender (male vs female), region (North America vs Western Europe vs Australia/New Zealand vs other), ECOG performance status at randomisation (0 vs 1), metastatic classification at randomisation (unresectable stage IIIC vs M1a vs M1b vs M1c and unresectable stage IIIC/M1a/M1b vs M1c), LDH at randomisation (normal vs elevated), brain metastases at baseline (no vs yes).

As the BRIM 3 study[9] is the only RCT investigating the efficacy of vemurafenib that is available, it was not possible to perform a meta-analysis. In addition to this, as BRIM 3[9] compared vemurafenib to dacarbazine in previously untreated BRAF V600 mutation positive patients, the manufacturer felt that an indirect comparison was unwarranted. The ERG agrees that it would not have been possible to perform a meta-analysis and that there were insufficient data to be able to perform a mixed treatment comparison.

4.2 Results

The planned interim analysis was performed in January 2011 based on a data cut from December 2010, when there had been 75 deaths (22%) in the dacarbazine arm and 43 deaths (13%) in the vemurafenib arm. The median OS was 13.2 months for patients receiving vemurafenib and 9.6 months for those receiving dacarbazine. The results of this interim analysis were presented to the data safety monitoring board (DSMB) for the study. The DSMB recommended release of the interim results based on compelling efficacy after determining that the p-value for the log-rank test for OS ($p<0.0001$) crossed the efficacy boundary in favour of vemurafenib. Because the OS interim analysis boundary was crossed, no additional formal hypothesis testing occurred after this point.

Two additional sets of analyses have since been performed (based on March 2011 and October 2011 data cuts). These analyses were carried out on the request of the FDA. As they were after statistical

significance of the OS benefit had been demonstrated, no formal hypothesis testing was involved. Table 8 shows the time-points of the OS analyses that have been performed to date.

Table 8 Timing of analyses

Data cut-off	Analyses performed	Reason for analysis
December 30, 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.
March 31, 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
October 3, 2011	Update of OS – no formal hypothesis testing occurred	Health authority request for further follow-up data to be included

Overall survival data are presented in Table 9 and as noted earlier these are confounded by that fact that patients were allowed to crossover to vemurafenib treatment following the interim analysis (data cut-off in December 2010).

Table 9: Overall survival BRIM 3[9] at various analysis time points

Data cut-off	Treatment	Number of deaths (%)	Non-censored hazard ratio (95% CI)	Censored hazard ratio* (95% CI)	Number of cross-over patients (%)
December 30, 2010	Dacarbazine	75 (22)	0.37 (0.26, 0.55)	N/A	0 (not applicable)
	Vemurafenib	43 (13)			
March 31, 2011	Dacarbazine	122 (36)	0.47 (0.35, 0.62)	0.44 (0.33, 0.59)*	50 (15%)
	Vemurafenib	78 (23)			
October 3, 2011	Dacarbazine	175 (52)	0.67 (0.54, 0.84)	0.62 (0.49, 0.77)*	81 (24%)

* Censored results at time of cross-over (MS pg 87)

The numbers of patients evaluable for each outcome based on the December 2010 data cut-off are presented in Table 10. The differences in the number of evaluable patients relates to the fact that patients required sufficient time to have been assessed for each outcome. In the case of PFS this was set at 9 weeks prior to the cut-off date and for BORR this was set at 14 weeks prior to the cut-off date. For OS, patients needed to have been randomised at least fifteen days prior to the cut-off date.

Table 10 Evaluable patients in December 2010 cut-off

	Includes patients randomised before	Vemurafenib (n=338)	Dacarbazine (n=337)
Evaluable for OS	15th December 2010	336 (99.41%)	336 (99.70%)
Evaluable for PFS	27th October 2010	274 (81.07%)	275 (81.60%)
Evaluable for BORR	22nd September 2010	220 (65.09%)	219 (64.99%)

Progression free survival and other response rates are presented in Table 11.

Table 11 Response rates – December, 2010

		Vemurafenib	Dacarbazine
Progression free survival (n=549)	Median progression free survival [months] (95% CI)	5.32 (4.86 to 6.57)	1.61 (1.58 to 1.74)
	Hazard ratio (95% CI)	0.26 (0.20 to 0.33)	
BORR (n=439)	Number of responding patients	106/219	12/220
	Response rate (95% CI)	48.4% (41.6% to 55.2%)	5.5% (2.8% to 9.3%)
Duration of response (n=439)	Median duration of response [months] (95% CI)	5.49 (1.22 to 7.62)	Not reached
Time to response (n=439)	Median time to response [months]	1.45	2.72

Exploratory efficacy analyses

As noted above, HRQoL data were collected using FACT-M questionnaires but response rates were low and the results have not been reported in the MS. [redacted] Pain scores and physical symptom improvement scores were also assessed but are not presented in the MS.

Further exploratory analyses were performed on patients with non-BRAF V600E mutations. According to the MS, a total of 19 patients out of 220 whose tumours were analysed by retrospective sequencing were reported to have BRAF V600K mutation positive melanoma. Although limited by the low numbers of patients, results were consistent with the main findings (OS, HR=0.27; 95% CI 0.05 to 1.51); PFS, HR=0.09 (95%CI 0.02 to 0.45); BORR: four responders among ten patients).

Per protocol analyses were also conducted but not reported in the MS. [redacted]

Sensitivity analyses

Stratified analyses of OS and PFS, as described earlier were performed but not reported in the MS. [redacted]

It was originally planned that a number of censored analyses would also be undertaken but these were not performed for a variety of reasons, Table 12 provides details on these.

Table 12 Reasons for not performing sensitivity analyses

Sensitivity analysis	Reason for not performing analysis
OS censored for potential subsequent use of vemurafenib in the dacarbazine arm	At the time of analysis patients in dacarbazine arm were not permitted to receive vemurafenib
OS censored for subsequent anti-cancer therapy	Compelling OS results observed at time of analysis
PFS censored for non-protocol anti-cancer therapy	Because there were so few patients evaluable for PFS who received anti-cancer therapy without disease progression, it was considered that this sensitivity analysis would not differ in conclusion from the primary analysis of PFS
PFS censored to account for missing visits	Only one patient satisfied criteria for missed visits.

Subgroup analyses

Subgroup analyses were performed for both OS and PFS, as described in section 0. Results for OS can be found in Figure 1 and results for PFS can be found in Figure 2.

Generally, results of subgroup analyses were consistent with the results of the main analyses. All subgroups were pre-specified, except for the combined metastatic classification at randomisation subgroup (unresectable stage IIIC/M1a/M1b). However, there were two further subgroup analyses specified in the SAP[15] that were not reported; BRAF mutation status (V600E vs other than V600E) and type of non-V600E BRAF mutation (V600D vs V600K vs V600R). Although the number of patients in these groups was small it raises concern as all subgroup analyses that were pre-specified should have been presented or reasons for not presenting them should have been provided.

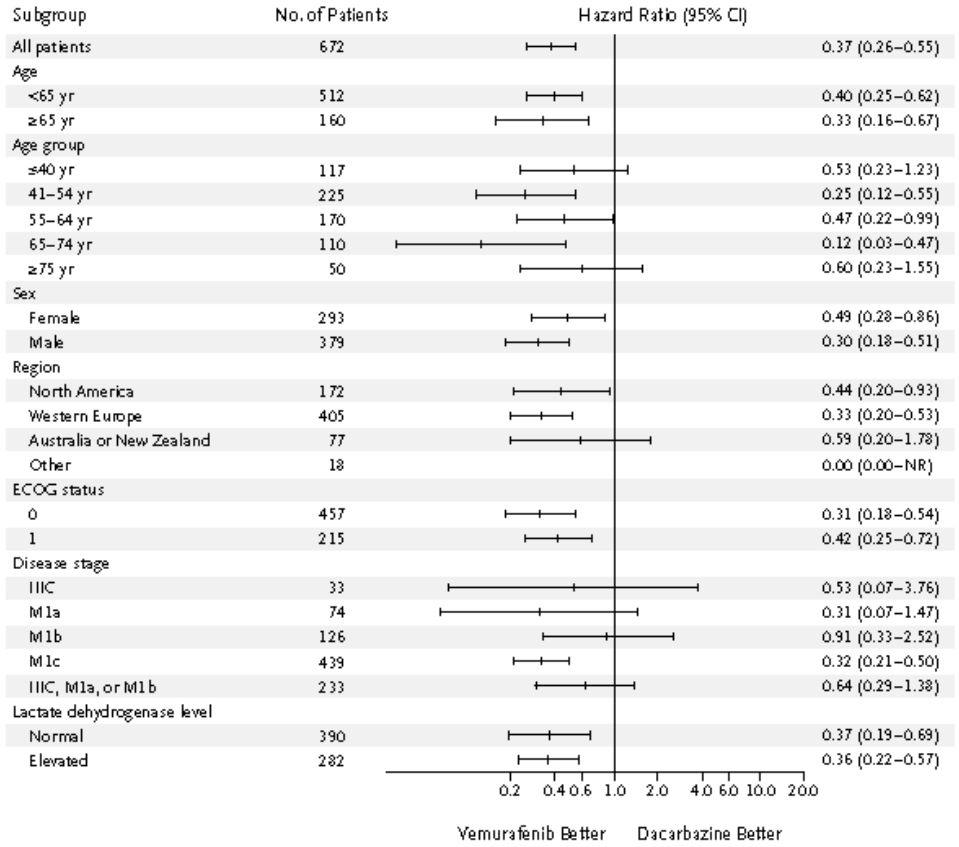

Figure 1 Subgroup analyses for OS

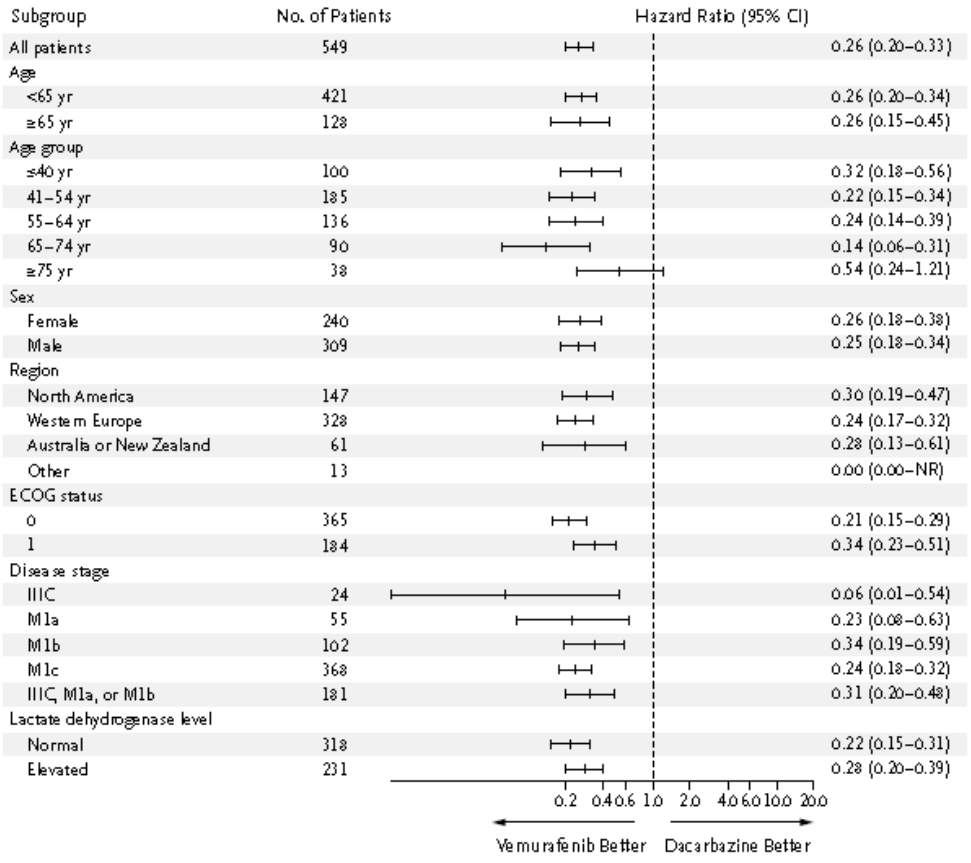

Figure 2 Subgroup analyses for PFS

Protocol deviations

Patients were recruited from 104 centres in 12 countries (United States, Canada, United Kingdom, France, Italy, Germany, Netherlands, Sweden, Switzerland, Israel, Australia and New Zealand). For the results of a trial with so many centres to be meaningfully interpreted, the manner in which the protocol is implemented should be clear and similar across all centres. This is because with so many investigators in different countries, general clinical practice will always be an issue and the results of a trial can only be generalisable if it is executed efficiently.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Adverse events

The MS points out that care needs to be taken in any comparison of AE rates related to the two arms of the trial due to the fact that treatment duration in the vemurafenib group spanned a period of 3.1 months, while for the dacarbazine patients it was only 0.76 months. Reported AEs of Grade 2 or more are reported in the published report of the trial[9] and are presented in Table 13. It is worth noting that these were recorded at the time of the interim analysis in December 2010.

Table 13 Grade 2 and above adverse events*– December, 2010

Adverse event[9]	Vemurafenib n=336	Dacarbazine n=282
	number of patients (%)	
Arthralgia		
Grade 2	60(18)	1(<1)
Grade 3	11(3)	2(<1)
Rash		
Grade 2	33(10)	0
Grade 3	28(8)	0
Fatigue		
Grade 2	38(11)	33(12)
Grade 3	6(2)	5(2)
Cutaneous squamous-cell carcinoma		
Grade 2	40(12)	1(<1)
Keratoacanthoma		
Grade 2	7(2)	0
Grade 3	20(6)	0
Nausea		
Grade 2	25(7)	32(11)
Grade 3	4(1)	5(2)
Alopecia		
Grade 2	26(8)	0
Pruritis		
Grade 2	19(6)	0
Grade 3	5(1)	0
Hyperkeratosis		
Grade 2	17(5)	0
Grade 3	4(1)	0
Diarrhoea		
Grade 2	16(5)	4(1)
Grade 3	2(<1)	1(<1)
Headache		
Grade 2	15(4)	4(1)
Grade 3	2(<1)	1(<1)
Vomiting		
Grade 2	9(3)	14(5)
Grade 3	4(1)	3(1)
Neutropenia		
Grade 2	1(<1)	4(1)
Grade 3	0	15(5)
Grade 4	1(<1)	8(3)
Grade 5	0	1(<1)

* Listed are all adverse events of grade 2 or higher that were reported in more than 5% of patients in either study group.

The MS provides slightly different figures and provides context related to those AEs that were of particular interest to patients. They note that 90% of patients experienced a skin or subcutaneous tissue disorder including rash (36%), alopecia (35%) and photosensitivity (30%). In addition patients presented with malignant and benign neoplasms. Skin papilloma was the most common appearing in 144 (43%) of patients and squamous cell carcinoma of the skin in 62 (18%) of patients. These events were considered as Grade 3 AEs. Lesions were excised and there was no interruption of treatment. The mechanisms that led to this increase in cutaneous neoplasms are currently under investigation.

The incidence of Grade 4 (life-threatening) AEs was low; only 14 (3%) of patients treated with vemurafenib experienced such events while 22 (8%) were recorded in the patients treated with dacarbazine. An overview of AEs and death from the October 2011 analysis is presented in Table 14.

Table 14: BRIM 3[9] Overview of adverse events and deaths (safety population)

Adverse events	**Vemurafenib n=336**	**Dacarbazine n=282**
	Number (%) of patients	Number (%) of patients
Any AEs	326 (97)	253 (90)
AEs of Grade 3 and above	168 (50)	86 (30)
AEs of Grade 3	163 (49)	74 (26)
AEs of Grade 4	13 (4)	22 (8)
AEs 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 AEs	110 (33)	45 (16)
Drug-related AEs	316 (94)	194 (69
Drug-related serious AEs AEs that led to discontinuation	88 (26)	15 (5)
AEs that led to dose modification/interruption	19 (6)	12 (4)

* 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
† Deaths were based on the all-treated population, where the N= 289 for dacarbazine and N = 336 for vemurafenib.
MS pg 124

Dose modifications were required in 159 (47%) patients treated with vemurafenib. Of these 112 (33%) had at least one dose reduction while 147 (44%) patients had one or more dose interruptions due to an AE. The mean number of days for such interruptions was eight (standard deviation (SD)= 6.2) with a range of one to 38 days.

The MS puts forward the case that dose modification and appropriate management of the AEs experienced with vemurafenib are worthwhile as the positive aspects of the treatment include rapid tumour response which is of value to patients. Clinical opinion provided to the ERG confirmed that these positive responses have been experienced by patients and are important to them and provide symptomatic relief.

It is worth nothing that a pharmacovigilance plan set by the EMA is in place to monitor AEs for patients receiving vemurafenib.[14]

Development of resistance

One of the exploratory analyses within the BRIM 3[9] trial was to evaluate biomarkers that may be relevant to the development of primary or acquired resistance to vemurafenib. The development of

resistance has been the topic of discussion and research with scientists actively pursuing strategies to overcome resistance (e.g. reactivation of the mitogen-activated protein kinase [MAPK]).[21] The mechanisms and effects of resistance to treatment are not yet clear and research in this area continues.[22,23]

4.3 Conclusions of the clinical effectiveness section

The manufacturer has sponsored all trials related to assessing the effectiveness of vemurafenib in the identified BRAF V600 mutation positive patients with malignant melanoma in both the first- and second-line treatment settings. The manufacturer identified three published trials[8,9,13] and bases the submission on a subgroup of patients identified in the NICE scope – those patients with previously untreated malignant melanoma. The MS has not presented a case for use in second-line treatment due to the current lack of robust trial data. The ERG understands their rationale and their decision to limit their submission. It is worth noting that the EMA marketing authorisation does not differentiate between patients who are treatment näive and those who have previously received treatment.

The BRIM 3[9] trial that provided data was well designed; however, based on requests from the approval authority (FDA), changes were made to the SAP that resulted in the single primary outcome of OS being amended to co-primary outcomes of OS and PFS. The data presented clearly demonstrate a statistically significant difference in favour of vemurafenib over dacarbazine in both OS and PFS in patients who have not received previous treatment for locally advanced or metastatic BRAF V600 mutation positive malignant melanoma.

Adverse events with vemurafenib are reported as manageable with dose modifications. Clinical feedback to the ERG indicates that this is consistent with their experience. In addition they agreed with the manufacturer's assertion that there was an early onset of symptom relief for patients when receiving vemurafenib.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by Roche in support of vemurafenib for the initial treatment of patients locally advanced or metastatic BRAF V600 mutation positive malignant melanoma. The two key components of the economic evidence presented in the MS are (i) a systematic review of the relevant literature and (ii) a report of the manufacturer's de novo economic evaluation. Table 15 contains details of the location of key information within the MS. The manufacturer has also provided an electronic version of their economic model which was developed in Microsoft Excel.

Table 15 Location of key economic information in the MS

Key information	Page number	Tables/figures
Details of the systematic review of the economic literature	133-136	
De novo analysis	136-143	Tables 29, Figures 24-25
Clinical evidence used in economic evaluation	143-187	Tables 30-32, Figures 26-56
Measurement and valuation of health effects	187-200	Tables 33-35, Figure 57
Resource identification, measurement and valuation	200-212	Tables 36-40, Figures 58-59
Methods of sensitivity analysis	213-224	Tables 41-43, Figures 60-62
Results - base-case analysis	224-229	Tables 44-51
Results - sensitivity analysis	229-247	Tables 52-54, Figures 63-65
Validation	247-248	
Interpretation of economic evidence	248-249	
Assessment of factor relevant to the NHS and other parties	250-252	Tables 55-57

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Objective of the manufacturer's cost-effectiveness literature review

The manufacturer's search was designed to evaluate whether de novo modelling was necessary in order to answer the decision problem set out in the scope. A full systematic review of cost-effectiveness studies in melanoma was conducted in support of the NICE technology appraisal for ipilimumab[11] and the manufacturer, therefore, focused their search on papers published following this review, i.e. from 9 December 2010 onwards.

On 17 January 2012 ProQuest was searched for databases Medline, EMBASE, and EMBASE Alert; EconLit was searched via the American Economic Association website; and NHS EED was searched using the University of York's Centre for Reviews and Dissemination website. All five databases were searched with the same set of search terms (see MS, Section 8.9, p273 for details).

The manufacturer appears not to have undertaken any searches of the unpublished literature; however, the ERG considers that finding any relevant studies from such sources is unlikely and concludes that the search strategy used by the manufacturer was appropriate.

5.1.2 Inclusion and exclusion criteria used in study selection

The inclusion/exclusion criteria used in study selection are presented in Table 16.

Table 16 Economic evaluation search inclusion and exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	BRAF V600 mutation positive advanced or metastatic melanoma patients	Non-melanoma patients; Non BRAF mutated patients
Intervention	Vemurafenib	-
Comparator	Dacarbazine; best supportive care, ipilimumab	-
Outcome	Cost per QALY gained; Cost per LY gained	-
Study design*	Economic evaluation (cost effectiveness analyses, cost utility analyses, cost minimisation analyses)	RCTs, observational data, budget impact assessments

*During the record sifting process records were excluded if they were not a cost-utility analysis

5.1.3 Conclusions of the review

The manufacturer's search of the published cost-effectiveness literature describing the use of vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation positive malignant melanoma did not identify any relevant cost-effectiveness studies. The ERG is satisfied with the manufacturer's search strategy and is reasonably confident that the manufacturer did not miss any relevant published articles.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Table 17 tests how closely the manufacturer's submitted economic evaluation accords with the requirements for a base-case analysis as set out in the NICE reference case checklist[24] and Table 18 summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond checklist.[25]

Table 17 NICE reference case checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by the Institute	Partial - the use of vemurafenib second line is not considered
Comparator(s)	Alternative therapies routinely used in the NHS	Yes – the comparator is dacarbazine
Perspective costs	NHS and Personal Social Services	Partial. The model only includes NHS costs. Personal Social Service costs have not been considered
Perspective benefits	All health effects on individuals	Health effects to the individual are captured via QALYs
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes	Yes – 30 year time horizon
Synthesis of evidence on outcomes	Systematic review	A systematic review was not undertaken. Survival data in PFS are taken from the BRIM 3 trial.[9] Data from the Roberts[26] trial and SEER registry[3] data are used to inform the modelling undertaken to project OS outcomes
Outcome measure	Quality adjusted life years	QALYs were used, which is appropriate
Health states for QALY	Described using a standardised and validated instrument	Quality of life data were not available from the BRIM 3[9] trial, therefore published QoL data were utilised. This is not ideal
Benefit valuation	Time-trade off or standard gamble	The standard gamble technique was used in both studies from which utility values were extracted
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	The Beusterien study[27] interviewed 63 members of the public and the Nafees study[28] interviewed 100. It is not clear how representative these individuals are of the public
Discount rate	An annual rate of 3.5% on both costs and health effects	Benefits and costs have been discounted at the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Sensitivity analysis	Probabilistic sensitivity analysis	Yes - deterministic, scenario and probabilistic analyses were undertaken by the manufacturer

QALY = quality adjusted life year; PFS = progression-free survival; OS = overall survival; QoL=quality of life

Table 18 Critical appraisal checklist for the economic analysis

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	The decision problem set by NICE included use of vemurafenib first and second line. The manufacturer only considered first-line use of vemurafenib. The ERG considers that this is appropriate.
Was a comprehensive description of the competing alternatives given?	Yes	The manufacturer described the chosen comparator (dacarbazine) adequately
Was the effectiveness of the programme or services established?	Partially	The effectiveness of vemurafenib Is established using data from the BRIM 3 trial[9], comprising PFS and OS data collected over approximately 15 and 22 months respectively. These limited data are used as the basis for projecting outcomes over a period of 30 years. There is thus considerable uncertainty about medium- and long-term outcomes for this patient group
Were all the important and relevant costs and consequences for each alternative identified?	Mostly	The ERG notes social care costs are not considered
Were costs and consequences measured accurately in appropriate physical units?	Partial	The ERG modified drug acquisition costs to reflect body weight and body surface area of a UK specific cohort of patients; the ERG is of the opinion that all drug administration costs should be estimated as day case costs; the ERG considers that, for patients who survive for several years, monitoring costs may be too high and utility values too low; additionally, in view of the fact that dose modifications were required in 47% of patients receiving vemurafenib the utility value associated with receiving vemurafenib during PFS may be optimistic
Were the cost and consequences valued credibly?		ERG considers that the manufacturer's estimates of OS lack clinical credibility and overestimate the effectiveness of vemurafenib
Were costs and consequences adjusted for differential timing?		Discounting should be undertaken annually but the manufacturer uses weekly calculations; the model includes a half-cycle correction which, although technically correct, may have minimal effect on model results due to the short (weekly) updating employed in the trial
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICER calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic, scenario and probabilistic sensitivity analyses were undertaken
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

PFS = progression-free survival; OS = overall survival; MS = manufacturer submission

5.2.2 Model structure

A schematic of the manufacturer's model is shown in Figure 3. It comprises three health states: PFS, progressed disease (PD) and death. All patients enter the model in the PFS health state. At the beginning of each time period patients can either remain in the same health state or progress to a 'worse' health state, i.e. from PFS to PD or death; or from PD to death.

The manufacturer states that the PFS state is designed to allow the modelling of the period in which some patients experience a response to treatment (with resultant tumour burden reduction) whilst other patients only experience disease stabilisation (lack of further disease progression), rather than response. The progressed disease state is designed to simulate the period of relatively low quality of life after first progression and prior to death.

Variants of this model structure have been used in the modelling of metastatic oncology for numerous NICE STAs (NICE TA227,[29] NICE TA212,[30]Fleeman et al 2010,[31] Hoyle et al 2011[32]).

The model has been developed in MS Excel and has a one week cycle length. It includes a half-cycle correction and the time horizon is set at 30 years. A discount rate of 3.5% has been used for both costs and outcomes and the perspective is stated to be that of the NHS and Personal Social Services.

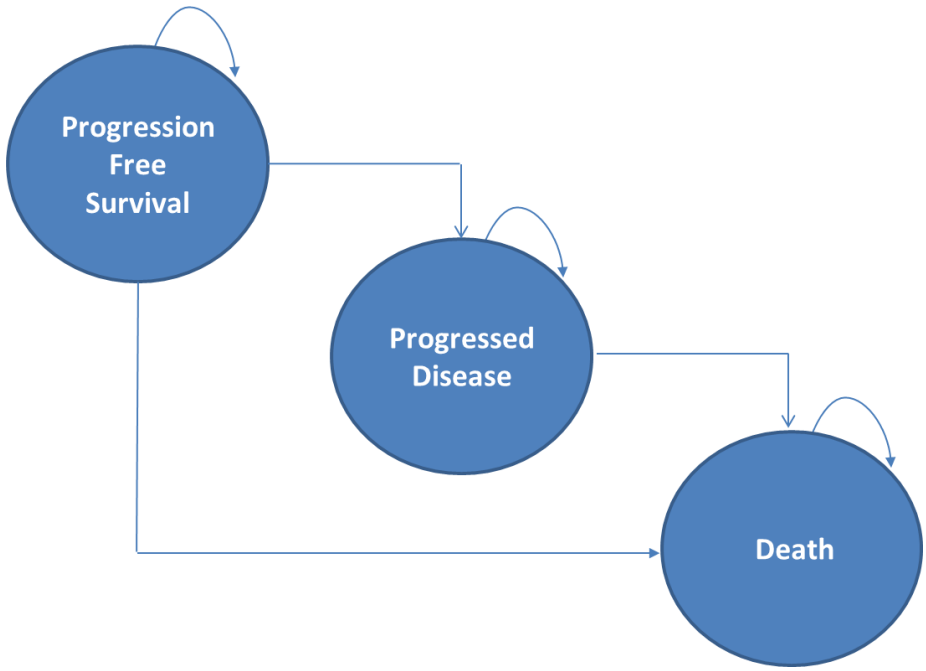

Figure 3 Schematic of manufacturer's model

5.2.3 Population

The economic model was constructed to evaluate the cost effectiveness of the use of vemurafenib for the first-line treatment of BRAF V600 mutation positive metastatic melanoma patients in England and Wales. The average (mean) age and body weight of patients in the BRIM 3 trial[9] are used in the model.

5.2.4 Interventions and comparators

Vemurafenib is modelled as administered in the BRIM 3 trial,[9] i.e. at a dose of eight 240 mg tablets daily. Four packs (56 tablets) are dispensed every 28 days, unless the dose is reduced due to AEs.

Dacarbazine is also modelled as administered in the BRIM 3 trial,[9] i.e. at a dose of 1000mg/m^2 every 3 weeks. Vial sharing was not modelled as the manufacturer considered that, due to the relatively low cost of the drug such modelling would have little effect on the size of the incremental cost effectiveness ratio (ICER).

Both drugs are administered until disease progression or unacceptable toxicity.

5.2.5 Perspective, time horizon and discounting

The manufacturer states that the economic appraisal is undertaken from the perspective of the NHS and Personal Social Services. The model does not include any social services costs, for example, the impact on social services of supporting people with malignant melanoma and their families. Outcomes are expressed in terms of gains in life years and quality adjusted life years (QALYs). The time horizon is set at 30 years and, in line with the NICE Methods Guide to Technology Appraisal,[24] both costs and benefits are discounted at 3.5%.

5.2.6 Treatment effectiveness and extrapolation

The model was developed using the March 2011 cut of the BRIM 3 data.[9] At that time cross-over was 7% (cross-over had increased to 24% by the October 2011 data cut). Progression-free survival and OS are modelled independently, and no relationship between the two is specified.

Progression free survival

The base-case model uses the probability of remaining in PFS observed in the BRIM 3 trial[9] directly for vemurafenib and dacarbazine until month 9 (week 39) and month 7 (week 30) respectively, after which survival for each intervention is extrapolated according to exponential functions. It is assumed that no deaths occur in PFS.

Table 19 PFS monthly hazard in curve tail

Variable	Value	CI	Reference in MS
Vemurafenib	0.2087	-	Section 6.3.1
Dacarbazine	0.2437	-	

Overall survival

Overall survival in the dacarbazine arm is based on three different sets of data. Firstly, the probability of OS observed in the BRIM 3trial[9] is used directly for 40 weeks (9.2 months). Secondly, following the observation that baseline characteristics and OS survival up to 10 months are very similar in the Robert[26] and BRIM 3[9] trials, the manufacturer assumes that longer term outcomes for BRIM 3[9] patients will match those of patients enrolled in the Robert trial.[26] The manufacturer split the cumulative hazard plot of the Robert trial[26] data into four phases (months 1-14; months 14-23; months 23-35; and months 35-46) and fitted different linear functions to each phase to allow a different (decreasing) hazard to be estimated for each of these time periods. Thirdly, as the Robert[26] data are only available up to month 46, further extrapolation to the tail of the simulated baseline risk curve was achieved by using a hazard estimate that allowed the 10-year survival landmark (9.1% alive) from the SEER registry[3] to be reflected in the model.

The vemurafenib arm was modelled by using the probability of OS observed in the BRIM 3[9] trial directly for the first 9.5 months and a hazard ratio representing differences between the vemurafenib and dacarbazine arms up to month 14, after which it was hypothesised that vemurafenib provided no further treatment effect so the hazards applied in the modelled dacarbazine arm were used in the vemurafenib arm from this point onwards.

For both arms (from week 200 onwards), if the risk of death associated with age/gender adjusted background mortality was higher than the hazard derived based upon the SEER[3] ten-year landmark figure then background mortality was used in the model.

Table 20 OS hazard in curve tail

Time (months)	Variable	Value	CI	Reference in MS
9-14	Vemurafenib	0.0761	-	Section 6.3.1
	Dacarbazine	0.0855	-	
14-23	Vemurafenib and dacarbazine	0.0658	-	
23-35	Vemurafenib and dacarbazine	0.0328	-	
35-46	Vemurafenib and dacarbazine	0.0141	-	
46 onwards	Vemurafenib and dacarbazine	0.001905	-	

5.2.7 Health related quality of life

FACT-M data were collected in BRIM 3;[9] however, completion rates were low and, as documented earlier, these data have not been publically reported. The manufacturer noted that a systematic search

had been undertaken to identify quality of life studies for the on-going ipilimumab STA.[11] The manufacturer therefore undertook a search to update this review but no further studies were identified. In their submission,[11] the manufacturer of ipilimumab had identified three sources, two of which were based upon mapping of information captured as part of their main RCT (the MDX010-20 trial, ipilimumab +gp100 vs gp100 vs ipilimumab[33]) using the EORTC QLQ-C30 and SF36v2 questionnaires, whilst the third (Beusterien et al[27])was a standard gamble study conducted in the UK and Australia (63/140 participants were from the UK). The vemurafenib manufacturer concluded that it would be most appropriate to use values from the Beusterien et al[27] study because:

- This study features a PFS utility value specific to patients experiencing a response to treatment (0.85 compared with 0.77 for a patient with stable disease).
- Clinicians advised that it might be inappropriate to use the quality of life post-progression value reported by Hodi[33] as some patients 'progressing' on ipilimumab (as defined by growth of their tumours) may, in fact, experience late response to treatment.

Beusterien[27] utility values were combined with the disutility associated with AEs to generate model utility values. The disutility associated with neutropenia that is used by the manufacturer is the value reported in a standard gamble study undertaken by Nafees et al[28] which focuses on the derivation of health state utility values and AE disutilities in metastatic non-small cell lung cancer. The manufacturer's clinical experts advised that it was reasonable to use this value for patients with advanced melanoma. Utility values extracted from the literature and adapted for use in the model are displayed in Table 21.

Table 21 Utility values

State	Utility value	CI	Reference
Model values			
PFS vemurafenib	0.806	Not derived	Derived using reported values [a], [b] and [c] (see MS p197)
PFS dacarbazine	0.767	Not derived	Derived using reported values [a], [b] and [d] (see MS p197)
PD	0.59	0.57 to 0.602	Beusterien, 2009[27]
Reported values			
PFS (Response) [a]	0.85	0.833 to 0.867	Beusterien, 2009[27]
PFS (Stable disease) [b]	0.77	0.755 to 0.785	Beusterien, 2009[27]
Skin reaction (rash) [c]	-0.03	-0.0296 to -0.0304	Beusterien, 2009[27]
Neutropenia [d]	-0.08973	-0.088 to -0.092	Nafees, 2008[28]

PFS = progression free survival; PD = progressive disease

5.2.8 Resources and costs

Intervention costs

Intervention costs are made up of the cost of vemurafenib and associated pharmacy costs. Vemurafenib is administered at a dose of 8 x 240 mg tablets each day until disease progression or unacceptable toxicity. However, trial data indicated that after 3 months only about 60% of patients received this dose. The cost used in the model has been estimated based on the pack price and the proportions of patients who were dispensed one, two, three and four packs at each dispensing date multiplied by the proportion of patients in PFS at each dispensing date (i.e. every 28 days).

The manufacturer has assumed that the time taken to dispense vemurafenib would be equal to that taken to dispense capecitabine (another oral chemotherapy agent), i.e. 12 minutes (Millar 2008[34]). No other administration costs are included.

As vemurafenib is indicated solely for patients who are BRAF V600 mutation positive, mutation testing is required. There is one European approved (CE marked) BRAF mutation test available (the 'cobas' test produced by Roche diagnostics). A single BRAF test costs £95 per patient tested (Roche diagnostics 2012[1]) which equates to a cost of £197.92 per BRAF positive patient identified, assuming a 48% mutation rate as reported by Long et al.[7]

Comparator costs

Comparator costs are made up of the cost of dacarbazine and the associated administration and pharmacy costs. Dacarbazine is administered at a dose of 1000mg/m^2 and the mean body surface area (BSA) in BRIM 3[9] was assumed to be 1.9141m^2. Dacarbazine can be purchased in1000 mg vials at a cost of £31.80 per vial (BNF62[35]). The cost used in the model is £63.60 (i.e. 2 x 1000 mg vials).

The manufacturer explains that although consideration of distribution of BSA around the mean would have produced a more accurate expected cost of dacarbazine, given the low cost involved only the mean value was considered in the model.

The manufacturer has assumed that the time taken to dispense dacarbazine would be equal to that taken to dispense oxaliplatin (another IV administered chemotherapy), i.e. 12 minutes (Millar 2008[34]). The administration time has been extracted from NHS Reference Costs 2009/2010.[36]

Intervention and comparator costs are summarised in Table 22.

Table 22 Intervention and comparator drug costs

Costs	Value	Source
Vemurafenib		
Drug cost	£1750 per pack (56 tabs)	Roche (MS)
Pharmacy cost	£13 every 4 weeks	Millar, 2008[34]
BRAF test	£95 per test (£197.92 per BRAF positive patient identified)	Roche diagnostics 2012[1]
Dacarbazine		
Drug cost	£63.60 per dose (given every 3 weeks)	BNF 62[37]
Administration cost	£248	NHS Reference Cost 2009/2010: SB12Z - Deliver simple parental chemotherapy at first attendance (outpatient)[36]
Pharmacy cost	£13 every 4 weeks	Millar, 2008[34]

Health care costs

Resource use in the economic evaluation is not derived from data collected as part of the BRIM 3[9] trial; rather the manufacturer has used the costs applied in the on-going NICE appraisal of ipilimumab.[11] The manufacturer's reasons behind the decision to use these costs are that they already appear to have been accepted by the ERG and Committee in that appraisal, and that their clinical experts felt that the costs used in the ipilimumab submission are likely to be applicable to vemurafenib.

Costs and sources for health state costs are displayed in Table 23.

Table 23 Health care costs

Health state	Value used in the ipilimumab STA[11]	Model value
Best supportive care in PFS	£378 per month	£87.30 per week
Best supportive care in PD	£378 per month	£87.30 per week
Terminal care cost	£5,408 (one-off)	£5408 (one-off)
Cost on disease progression	£648 (one-off)	£648 (one-off)
Palliative care (four months before death)	£838 per month	£3352 (one-off)

PFS= progression-free survival; PD = progressive disease

Adverse event costs

Only those AEs occurring in greater than 5% of patients at Grade 3/4 severity are incorporated into the model. All AEs are assumed to occur during the first year of treatment and are applied as a one-off, undiscounted, cost. Costs for AEs, and their sources, are displayed in Table 24.

Table 24 Key model parameters: adverse events

Adverse event	Incidence	Cost per episode	Source
Rash	8.33% in vemurafenib arm	£126.96	Roche 2006[1] uplifted using PSSRU[38] HCHS inflation index
Neutropenia	8.5% in dacarbazine arm	£407.38	Roche 2006[1] uplifted using PSSRU[38] HCHS inflation index
CuSCC/Keratocanthoma	14.29% in vemurafenib arm	£115	NHS Reference Costs 2009/2010[36]- JC03C: Outpatient major skin procedure category 1 without cc

5.3 Cost-effectiveness results

The base-case incremental results generated by the manufacturer's model are presented in Table 25. The ICERs for the target population are £94,267 per QALY gained and £64,891 per life year gained. The ERG notes that the ICER exceeds NICE's perceived cost per QALY threshold. A summary of predicted resource use by category of cost is presented in Table 26.

Table 25 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) (cost/ LY)	ICER (£) (cost /QALY)
Dacarbazine	[redacted]	[redacted]	[redacted]					
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,267
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 26 Summary of predicted resource use by category of cost for the base case

Unit Cost	Vemurafenib	Dacarbazine	Increment	Absolute increment	% absolute increment
Drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pharmacy/ Admin	[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 Testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse events; PFS= progression-free survival; PD = progressive disease; BSC=best supportive care

5.4 Sensitivity analyses

Deterministic sensitivity analyses

The manufacturer varied transition probabilities (± 10%), with the exception of the monthly hazard of death from month 46 onwards which was varied ± 50%, utilities (± 10%), costs (between upper and lower CI assuming the standard error =1/4 base case value), patient characteristics (age ± 10 years) and BRAF mutation incidence 40-60%), and general parameters (time horizon (-20 years) and discount rates (0% and 6%)). The results, presented in Table 27, for the ten parameters showing the greatest variability, demonstrate that the ICER per QALY gained for vemurafenib in the modelled patients is most sensitive to discount rates and hazard of death between months 9 and 14.

Table 27 Deterministic univariate sensitivity analysis results

Parameter	Base-case value	Low value	High value	Low value ICER/QALY	High value ICER/QALY
Health outcomes discount rate	3.5%	0%	6%	£70,358	£110,535
Both discount rates	3.5%	0%	6%	£73,397	£108,090
Monthly hazard of death (vemurafenib) - month 9-14	0.0761	-10%	+10%	£87,279	£102,283
Monthly hazard of death (dacarbazine) - month 9-14	0.0855	-10%	+10%	£100,775	£88,808
Time horizon	30 years	20 years	-	£103,793	-
Monthly hazard of death (both) - month 14-23	0.0658	-10%	+10%	£90,977	£97,618
Costs discount rate	3.5%	0%	6%	£98,346	£92,178
Resultant PFS utility values	Vem = 0.806 Dac = 0.767	Dac PFS utility (0.767) applied to both treatments	Vem PFS utility (0.806) applied to both treatments	£98,339	£96,070
Age	54	45	65	£93,071	£94,584
Monthly hazard of death (both) - month 23-35	0.0328	-10%	+10%	£92,290	£96,258

Vem=vemurafenib; Dac=dacarbazine; PFS=progression free survival; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years

Further analyses were carried out around the model used to predict OS and utilities. The results from these analyses are presented in Table 28.

Table 28 Scenario analyses results

Description	ICER per QALY gained
Base case	£94,267
Overall survival	
October cut of BRIM 3[9] data	£128,060
Base case with 34 month treatment effect	£77,343
Utility estimates	
Base case with higher Hodi mapped PD utility value used to reflect the potential for patients in 'tail' of survival curve to have lower tumour burden and therefore improved HRQoL	£82,017
Hodi[33] EORTC-QLQ-C30 mapped values	£83,643
Hodi[33] SF-36 mapped values	£103,345

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years

Probabilistic sensitivity analyses

The manufacturer undertook probabilistic sensitivity analysis (PSA) to derive the mean ICER of vemurafenib vs dacarbazine. The distributions used in the PSA have not been provided. The manufacturer notes that OS, the parameter subject to the most uncertainty, was not varied probabilistically as they were not able to determine which potential extrapolations should be given a higher likelihood of occurring. The manufacturer highlights that this omission means that the PSA significantly understates the uncertainty associated with the incremental QALY gain provided by vemurafenib.

In the 3000 simulations conducted by the manufacturer vemurafenib would be considered cost effective in 0% of simulations up to the value of £15,000 per QALY gained. At a threshold of £100,000 per QALY gained vemurafenib would be considered as being cost effective in 96.9% of simulations. The cost-effectiveness plane and cost-effectiveness acceptability curve included in the MS are reproduced in Figure 4 and Figure 5 respectively.

5.4.1 Model validation and face validity check

The manufacturer states that the model was validated by a health economist not involved in the development of the submission. This health economist checked the model's functionality and noted only minor errors which were subsequently corrected. In addition, the extrapolation conducted was discussed with an academic health economist and a panel of clinicians who felt that whilst subject to uncertainty the extrapolation approach employed appeared reasonable given the evidence currently available.

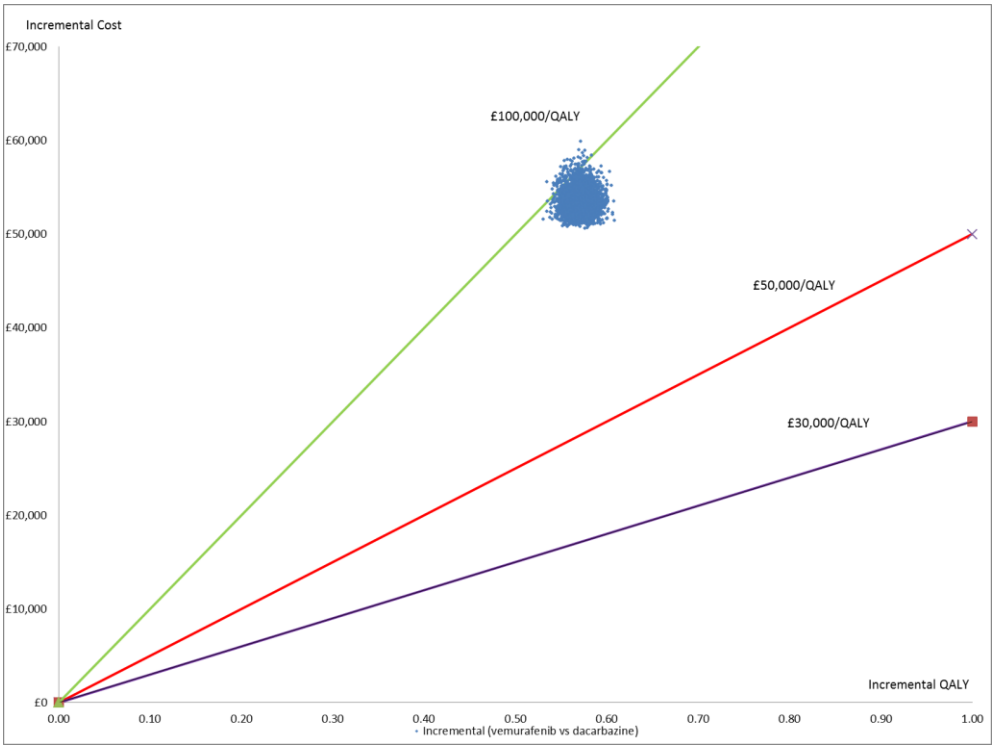

Figure 4 Cost-effectiveness plane for vemurafenib vs dacarbazine

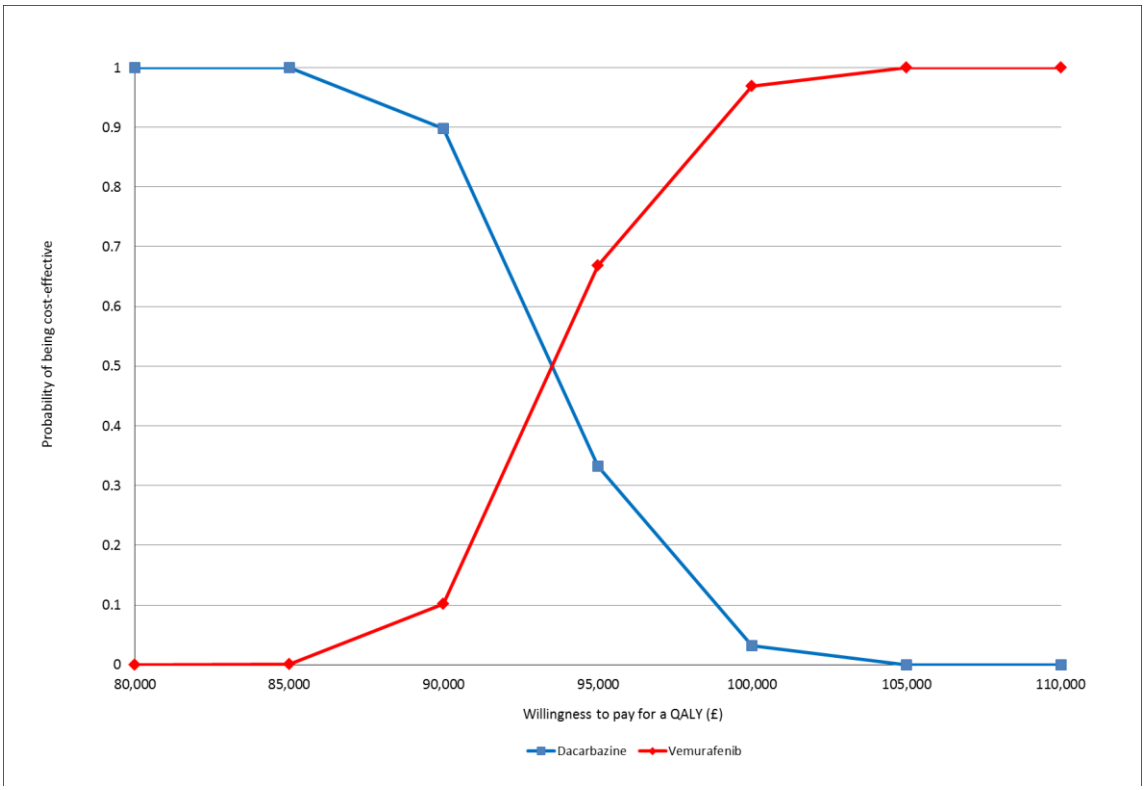

Figure 5 Cost-effectiveness acceptability curves for vemurafenib vs dacarbazine

5.5 Detailed critique of manufacturer's economic model

5.5.1 Model design and implementation

The manufacturer's model is implemented as a series of Microsoft Excel worksheets. The layout of the model is generally clear and tables are adequately labelled. The manufacturer has adopted a simple three-state model design, adapting a model structure previously used in several submissions to NICE appraisals of cancer drugs. The model is driven by survival models governing PFS and OS which are updated at weekly intervals. These are calibrated against data from the BRIM 3[9] trial combined with selected results from the Robert trial[26] and published analyses of the SEER registry[3] data. Patients alive post progression (PPS) are estimated as the difference between OS and PFS.

It should, however, be noted that the idea of 'progressive disease' in malignant melanoma as a single absorbing health state may not be appropriate. For example, on occasions skin lesions may appear to develop and then later spontaneously improve. It is generally acknowledged that the patient population is heterogeneous, with the majority of individuals dying relatively quickly (less than 12 months) but with a small proportion benefitting from extended survival with few if any overt symptoms. The manufacturer has employed a sequence of modelling approaches attempting to capture this phenomenon. However, the ERG has serious reservations about the methods used for survival projection, and the lack of any underlying rationale.

The model employs a mid-cycle correction for calculation of state-based costs and outcomes. This is technically correct, though with short (weekly) updating it is arguable that this is likely to have had a minimal effect on model results.

Cost to pathology in terms of supporting the BRAFV600 testing has not been considered. The ERG consider that the costs of testing may have been underestimated, though we cannot say by how much and true costs are likely to make the ICER for vemurafenib vs dacarbazine worse.

5.5.2 Cost estimation and parameter values

Discounting costs and outcomes

In the submitted model the adjustment for discounting both costs and outcomes has not been correctly applied. In classical economic theory discounting is used continuously with costs and benefits discounted from the date they are incurred. However in UK NHS practice, discounting is normally applied annually to conform to the annual accounting cycle and the annual calculation of NHS Reference Costs. In the model, events and costs are discounted weekly, using fractions calculated based on the number of weeks in a year. Correcting this issue results in a revised ICER that is £484 lower per QALY gained than the manufacturer's base-case ICER.

Active treatment costs

The ERG has re-estimated the costs of therapy based on the distribution of patient body weight and BSA of a UK specific cohort of patients,[39] rather than the use of a simple average based on trial data. Overall this change decreases the drug costs in the dacarbazine arm by £12 per patient and increases the cost per QALY gained by £22 per patient compared with the manufacturer's base case ICER. If NHS contract prices (eMit)[40] are used in place of list prices, the reduction in dacarbazine cost per patient is £86 and the ICER increase from the base case is £149 per QALY gained.

In the manufacturer's model, dacarbazine treatment is assumed to be administered as an out-patient attendance at a cost of £248. It is more likely to be delivered in an oncology day case unit at a national average cost of £207 per session (HRG SB12Z for NHS Trusts chemotherapy delivery: day case - NHS Reference Costs 2009/10[41]). Applying this reduced unit cost results in a reduction of £218 per patient treated with dacarbazine, and an increase in the base case ICER of £380 per QALY gained.

Long-term monitoring costs

Clinical advice to the ERG indicates that long term monitoring of patients will vary. For those whose disease progresses quickly the monitoring period will be relatively short as their conditions are likely to deteriorate quickly. For patients whose disease has progressed but nonetheless continue to survive for several years, the manufacturer re-uses a cost estimate (£378 per month) previously commissioned by the manufacturer of ipilimumab. The ERG questions whether a single cost is applicable indefinitely for patients whose disease remains stable and largely symptom-free. Clinical advice proposes that monitoring (consisting of a CT scan and out-patient visit to an oncologist) would initially be required 3 to 4 times per year for 2 years, reducing to twice a year for 2 years, and finally annually thereafter. In addition, GP consultations are proposed at frequencies of four times, three times and twice per year in these time periods. The corresponding annual monitoring cost estimates are then £1089, £645 and £339 respectively.

Applying these revised costs to the manufacturer's model results in a net reduction in incremental cost per patient of £520, and a corresponding reduction in the base-case ICER of £907 per QALY gained.

5.5.3 Utility estimation and parameter values

Utility associated with adverse events

Data from the BRIM 3 trial[9] (MS, p118) indicates that the number of AEs is high, with AEs leading to dose modification or interruption in 38% of patients in the vemurafenib group compared with 16% in the dacarbazine group. It is noted that there were very few AEs recorded as being of Grade 3 or higher; however, if the level was sufficiently high to lead to dose reduction then it is anticipated that the AE would be accompanied by a certain level of disutility. Clinical advice indicates that low grade but rather chronic toxicity is common with oral TKIs and that the symptoms are manageable with

dose reductions. Dose reduction is preferred to stopping the treatment due to the response noted by patients. It is recognised that quality of life data, although collected, are not available from the BRIM 3 trial.[9]. However, as the number of patients whose dose was reduced or interrupted in the vemurafenib arm is more than twice that in the dacarbazine arm, the PFS utility benefit generated by the model for the vemurafenib arm may be optimistic.

Utility during post-progression survival

The manufacturer has used a utility value of 0.59 for all patients in PPS. This value is taken from Beusterien et al[27] and appears to be based on an assumption of median survival of 8 to 10 months and may be too low bearing in mind the long survival times of some patients. If it is assumed that all patients with OS greater than 5 years have a long-term utility that is equivalent to PFS stable disease (i.e. 0.767) then the ICER per QALY gained for vemurafenib is reduced to £82,664 per QALY gained (a reduction of £11,603).

5.5.4 Estimation of patient outcomes

Progression-free survival

The ERG has carried out its own analysis of the March 2011 PFS data from the BRIM 3 trial,[9] projecting hazard trends, and has obtained an estimated mean value for PFS very similar to that generated by the manufacturer's model.

Overall survival

The method of extrapolation used by the manufacturer to project OS from the observed BRIM 3[9] data (up to 10-12 months) out to 30 years is extremely elaborate, involving three different sources, six time phases and multiple assumptions each of which is vulnerable to challenge. The ERG notes the industry involved in its development but is concerned that resultant extrapolation appears to lack a coherent underlying and compelling logic connecting the natural history of the disease, the mode of action of the interventions, and the accumulated experience of clinicians and patients. In summary, it focuses on accurate *description* of the available information at the risk of compromising the credibility of any *projections* produced.

Several apparent assumptions can be contested, namely that:

- a hazard ratio estimated from the BRIM 3[9] data can be applied to extend the treatment effect of vemurafenib to 14 months

- results from the latter part of one arm of the Robert[26] trial (based on 78 patients) provides a reliable basis for modelling the experience of both dacarbazine and vemurafenib patients beyond 14 months of survival to 45 months

- long-term survival beyond 45 months can be adequately represented by a single mortality risk parameter calibrated to reconcile Robert[26] trial data with a single value from the SEER[3] database analysis at 10 years. In doing this they ignore the SEER [3] hazard profile which was based on the experience of over 1000 patients.

The evident weaknesses of the approach used in the MS to projecting long-term benefits of vemurafenib led the ERG to examine the BRIM 3 trial[9] evidence closely, and to develop an alternative model which suggests the manufacturer has substantially over-estimated the likely gains attributable to vemurafenib. This work is described below, and offers some observations relating to the way survival gains are generated and limited, which may be tested in future clinical research.

5.6 ERG exploratory analysis

5.6.1 Understanding the effect of vemurafenib on overall survival

It is clear from examination of the Kaplan-Meier OS plots for analyses of data from the BRIM 3[9] trial that patients receiving vemurafenib experience an early advantage compared with those receiving dacarbazine. This is seen most clearly from the cumulative hazard charts, which indicate that no assumption of proportional hazards can be made when comparing overall results from the two trial arms. However, there is an equally straightforward mechanism which can explain the observed results; this assumes that vemurafenib is very effective at suppressing disease progression leading to death at the beginning of the trial, but after a short period this effect ceases to operate, and patients revert to the pattern of mortality risk seen in the dacarbazine arm.

This hypothesis is easily tested by shifting the dacarbazine hazard plot forward in time until it matches, as far as possible, the vemurafenib trend (excluding the initial period when both drugs are coming into full effectiveness prior to the long-term trend becoming established). This procedure was carried out on both the March and October 2001 BRIM 3[9] data cuts, and the optimal temporal shift was found to be 97 days.

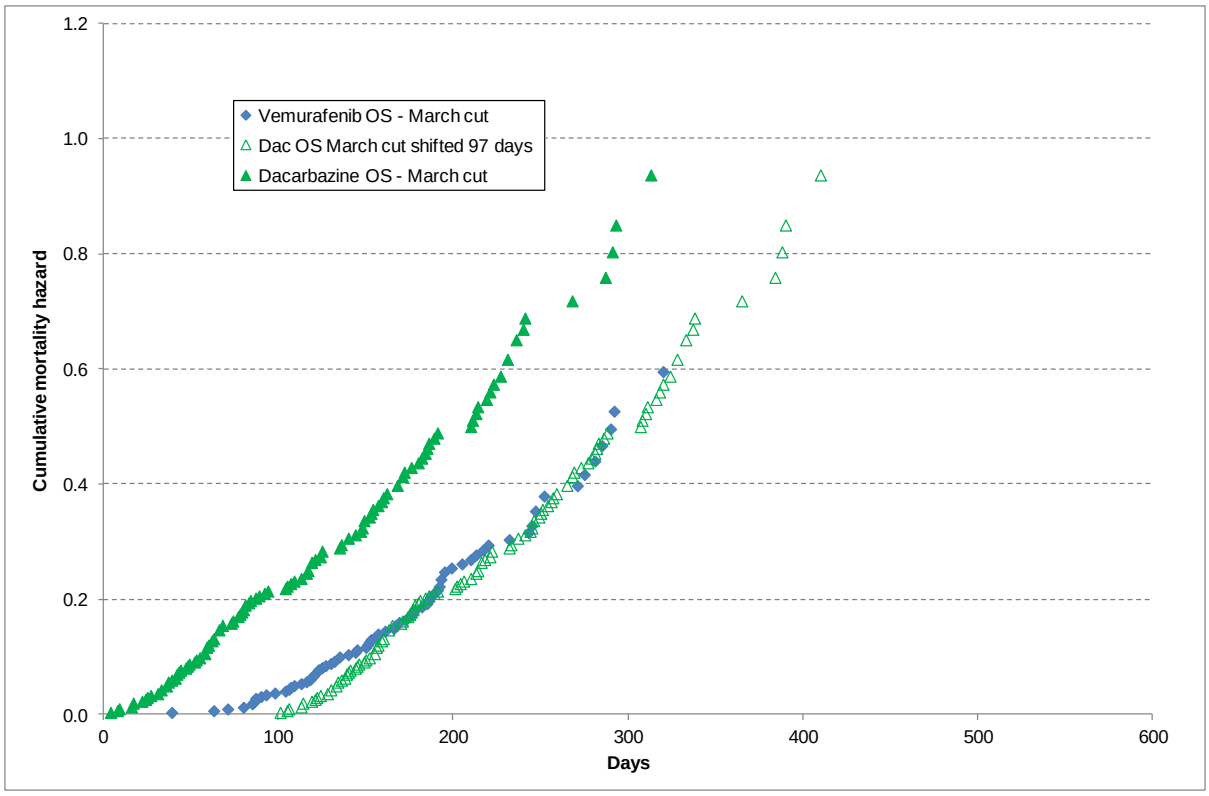

Figure 6 Effect of shifting dacarbazine cumulative hazard plot forward by 97 days (BRIM 3[9] March data cut off)

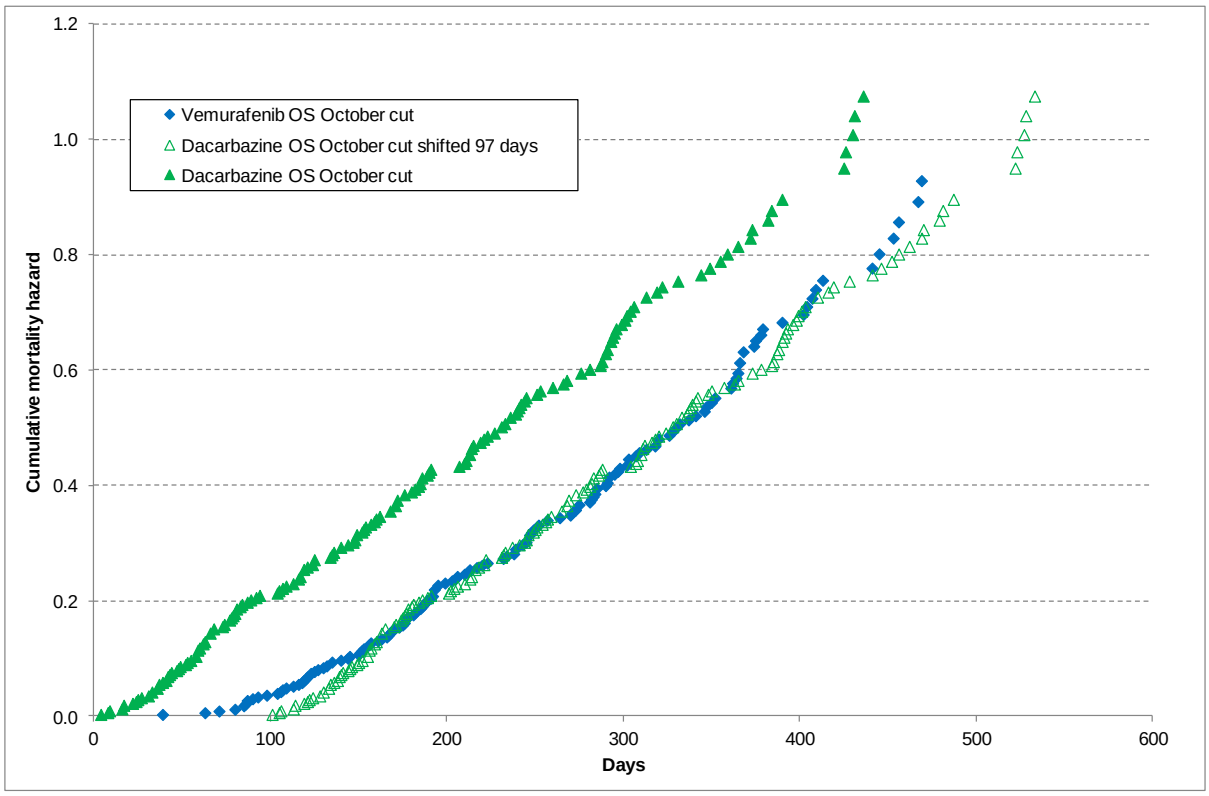

Figure 7 Effect of shifting dacarbazine cumulative hazard plot forward by 97 days (BRIM 3[9] October cut off)

Figure 6 and Figure 7 show the results obtained which indicate a strong correspondence between the vemurafenib and shifted dacarbazine trends in both data sets. This indicates that the simplest interpretation of the trial evidence is that vemurafenib is effective in suppressing mortality for only a limited period (on average about 97 days) after which it no longer provides any survival benefit compared with dacarbazine. Since the same effect occurs in both data sets it suggests that the effect is independent of any crossover effect, or that crossover of patients from dacarbazine to vemurafenib has no effect on OS.

A rationale for such a limited window of effectiveness is provided by the observation that resistance is common with all new TKI drugs, reflecting the fact that cancer cells use multiple signalling pathways, and that when one is blocked others will come into play.

5.6.2 Understanding the nature of long-term survival in malignant melanoma

In considering the long-term prognosis of patients with malignant melanoma, it is important to use the most complete and detailed registry analysis available. In this case the analysis reported by Balch,[6] which formed the basis for the final 2009 AJCC[42] melanoma staging and classification system, provides the results of sub-classifying metastatic melanoma on the basis of differential survival into four categories (M0, M1a, M1b, M1c in order of reducing expected survival). This study employed data from 7635 patients with metastatic disease at diagnosis and is therefore the most extensive source of relevant information for the population considered in this appraisal. In order to make use of the AJCC database findings it was necessary to digitize the published survival curves, and then construct a case-mix adjusted survival curve based on the relative proportions of patients in the BRIM 3 trial[9] (15.9% M0/M1a, 18.8% M1b, 65.3% M1c) (MS p52).

The observation is made by clinicians that there appear to be two quite different population 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 much better prospects and who, in some cases, can survive for 10 years or more with a relatively good HRQoL. Unfortunately, at present, no indicators have been identified which distinguish between these two groups. In order to replicate the patterns of survival reported by Balch et al[6] the ERG attempted to explore the potential of the simplest survival model which might match these criteria. This assumes that there are two sub-groups of patients split in an unknown ratio, and that each sub-group is governed by a separate long-term mortality risk (equivalent to an exponential survival function).

The results of calibrating such a compound survival model against the BRIM 3[9] case-mix adjusted AJCC survival curve are shown in Figure 8 and indicate a very close correspondence. The fitted model results in 80.6% of patients having a mean survival of 11 months (0.91 years), and 19.4% of patients benefitting from an expected mean survival of over 12 years (145 months).

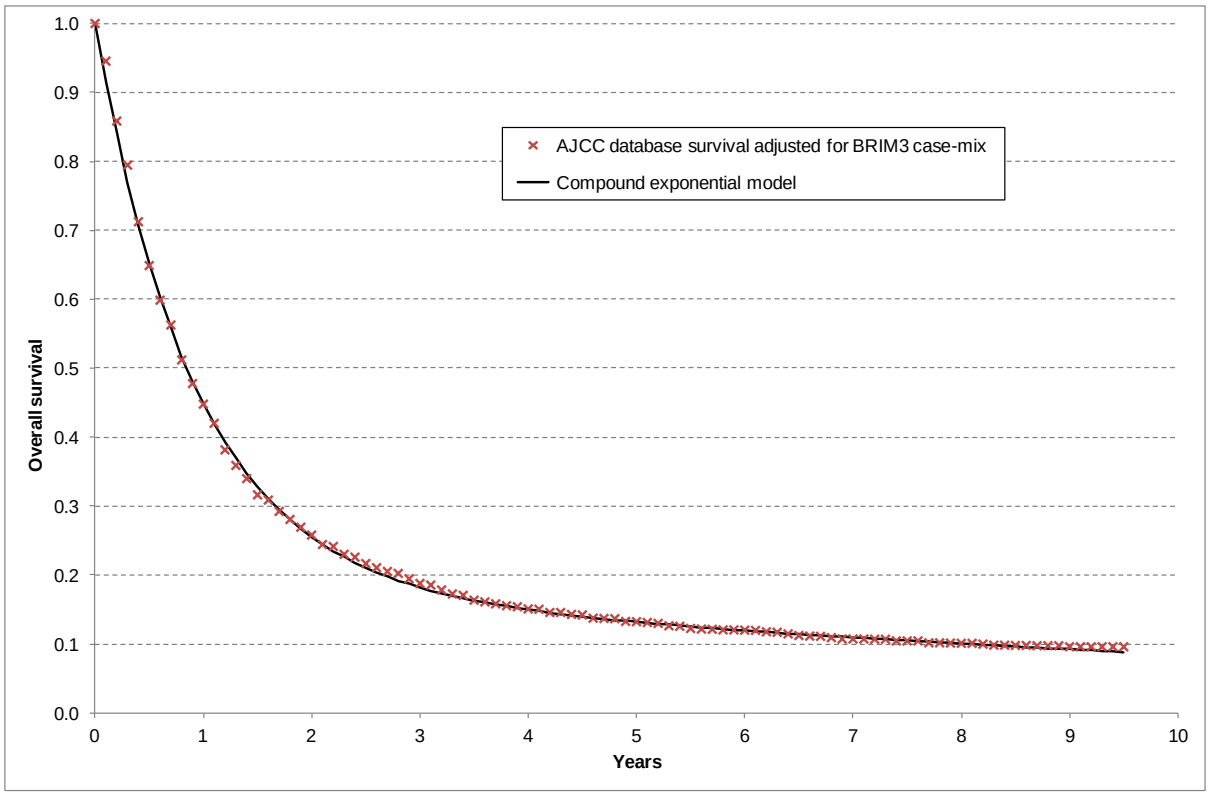

Figure 8 Compound exponential survival model (two subgroups) fitted to AJCC malignant melanoma data case mix adjusted to match the BRIM3[9] population

On the principle of modelling parsimony this appears to be a simple 3 parameter long-term survival model appropriate for projecting BRIM 3 trial[9] results in an economic model. Combining this formulation with the BRIM 3 trial[9] data allows for a simple common projection method beyond the observed trial data preserving the estimated OS difference of 97 days in favour of vemurafenib described above. Figure 9 illustrates the close correspondence between BRIM 3[9] results and the proposed model for both treatments.

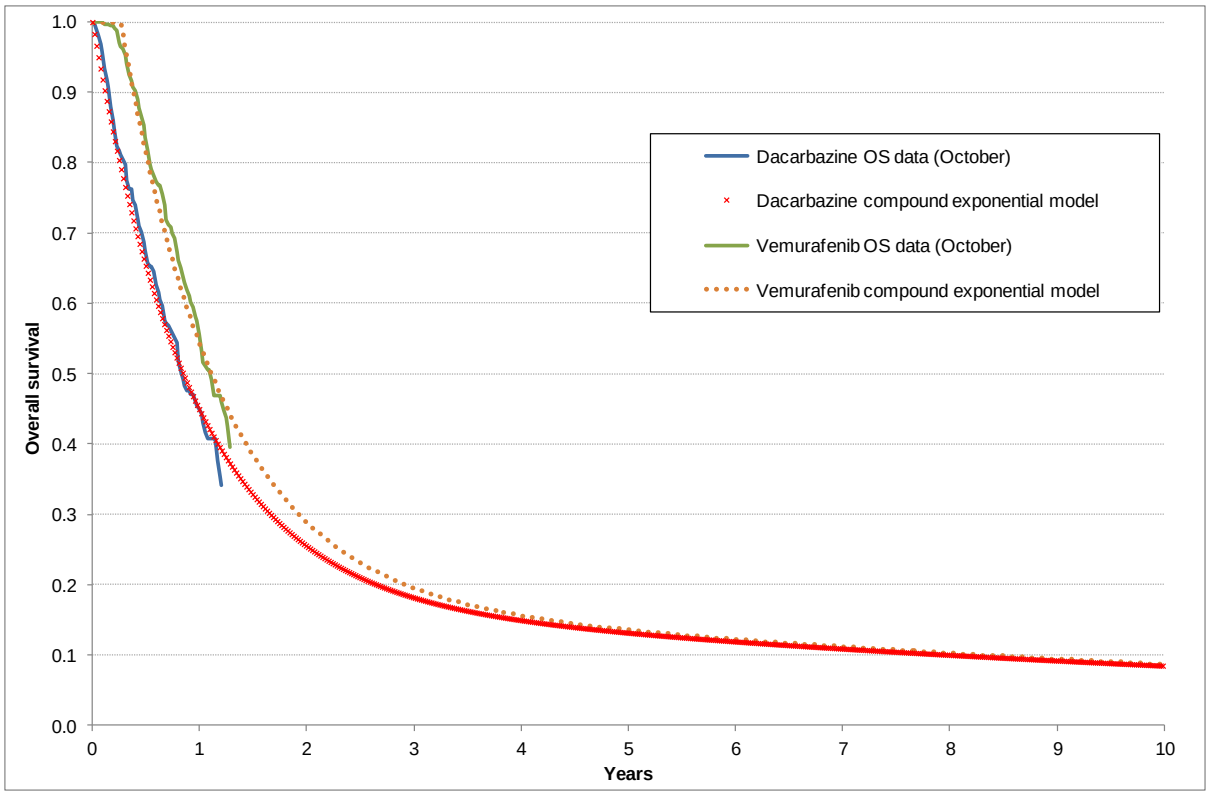

Figure 9 Compound projection OS models compared with BRIM 3 trial[9] OS results

5.7 Conclusions of the cost-effectiveness analysis

The manufacturer's search of the published cost-effectiveness literature describing vemurafenib vs dacarbazine for the treatment of patients with locally advanced or metastatic BRAF V600 mutation positive malignant melanoma did not identify any relevant cost-effectiveness studies. The ERG is satisfied with the manufacturer's search strategy and is reasonably confident that the manufacturer did not miss any relevant published articles.

The manufacturer's reported base-case ICER for vemurafenib vs dacarbazine is £94,267 per QALY gained. The ERG has identified a number of amendments and corrections to the manufacturer's economic model. The individual and combined effects of implementing these changes are shown in Table 30 The single most important factor in increasing the ICER is the ERG's estimation of OS gain limited to just 97 days. If this change were not accepted then the revised base-case ICER would fall to only £81,791 per QALY gained.

Table 29 Revised base-case cost-effectiveness analysis, incorporating corrections and amendments identified by the ERG

	Dacarbazine			Vemurafenib			Incremental			ICER
	Cost per patient	Life years per patient	QALYs per patient	Cost per patient	Life years per patient	QALYs per patient	Cost per patient	Life years per patient	QALYs per patient	Cost per QALY gained
Manufacturer's base case analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£94,267**
Correct discounting logic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,783
Amend dacarbazine admin. costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,646
Amend post-progression utility value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£82,664
ERG estimate of dacarbazine costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,289
Amend long-term monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,360
ERG overall survival model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£230,175
Revised base case analysis with all ERG changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£226,144**

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Additional analysis: early termination of vemurafenib treatment

The ERG requested results of an analysis designed to compare the outcomes in the BRIM 3 trial[9] of patients continuing on treatment with vemurafenib until disease progression or death with those terminating treatment prior to disease progression or death.

The context of this request is the recognition that treatments given continuously until disease progression or death, whilst initially producing measurable response and improved HRQoL, may be continued even after they have ceased to provide additional benefit. Where this occurs continued treatment will incur unnecessary costs, and may result in chronic treatment-related AEs, which also impact on both HRQoL and cost. This general concern is reinforced by the data analysis already described, indicating that vemurafenib may have delivered only a restricted survival benefit rather than an indefinite mortality advantage.

To test this proposition within the limitations of the BRIM 3 trial[9] data, the ERG considered it would be helpful to compare outcomes (PFS and OS) 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 is no difference in outcomes it may suggest that patient benefit no longer continues to accrue after an initial period on therapy.

[redacted]

If it proves possible to determine a maximum effective duration of vemurafenib treatment in this patient population then it would have an important bearing on the assessment of cost effectiveness. The extent of this effect is illustrated in Table 30 where there is a reduction in the estimated ICER per QALY gained of nearly 40% if treatment is restricted to a maximum of five prescriptions.

[redacted]

[redacted]

[redacted]

Table 30 Revised base-case cost-effectiveness analysis, incorporating corrections and amendments identified by the ERG related to days of treatment

	Manufacturer's base case		with ERG changes	
Maximum vemurafenib treatment period (days)	**Cost of vemurafenib & admin**	**ICER per QALY gained**	**Cost of vemurafenib & admin**	**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]	**£226,144**

6.2 Additional analysis: manufacturer objections to selected sub-group analysis

The ERG requested results of an analysis of outcomes in the BRIM 3 trial[9] for a subgroup of patients who survived for at least one day beyond disease progression; Kaplan-Meier survival analyses of PFS and PPS were requested in these patients by trial arm. The main objective was to investigate whether there is any evidence from the pivotal trial supporting the notion that vemurafenib continues to yield survival gains after the treatment is discontinued.

The manufacturer raises strong arguments against the legitimacy of this analysis in its clarification response, under two headings. Firstly, it is pointed out that **imbalances in the baseline characteristics** of patients in this subgroup confound any results obtained:

"The vemurafenib group includes more patients with elevated LDH, more patients over the age of 65, a higher proportion of female patients, more patients diagnosed with metastatic disease and less patients in the best Performance Status category. Each of these imbalances favours the dacarbazine arm, with the result that any comparison of the outcomes of patients in these two post-hoc defined groups will be heavily confounded by these imbalances, and any subsequent extrapolation of the post-progression outcomes on the whole population based on this subgroup would be biased."

The ERG recognises that this is an important area of concern, but believes that the case may have been overstated by the manufacturer in several respects:

- comparisons of the balance of patient characteristics between treatment arms for each of these factors has been carried out using the Chi-squared test, and none show differences at conventional levels of significance (i.e. the variations are consistent with random selection). This is not conclusive, but supports the view that any numerical difference must also be clearly shown to have a relatively strong influence on outcomes before it becomes a cause for concern.

- the age of patients was not a stratification variable for the BRIM 3 trial,[9] and there was a marked difference in the proportion of older patients (over 65) between the trial arms, with 7.5% more in those randomised to vemurafenib compared with dacarbazine in the ITT population. In fact, the ERG specified subgroup is markedly better balanced, with a difference of only [redacted]

- gender was also not a stratification variable for the BRIM 3 trial,[9] and was not well balanced in the ITT population (5.8% more males in the vemurafenib arm), and this imbalance is increased to [redacted]in the specified subgroup. However, the SEER database analysis reported by Xing et al[3] shows that in Stage IV melanoma patients the hazard ratio for male gender is only 1.08 and non-significant in multivariate Cox regression analysis, suggesting that this difference is unlikely to have a major influence:

"By testing whether the trends of the survival curves were different among various subgroups (i.e. age, race, sex, histology, and tumor location).... none of the variables were determinates of conditional survival improvement for the cohort with stage IV disease."

- ECOG performance status, disease stage and LDH status were stratification variables in BRIM 3[9] and therefore accurately balanced in the ITT population, and some imbalances are inevitable in any subgroups. However, it is important to recognise that stage and LDH status are not separate classifications as patients with elevated LDH are automatically coded as stage M1c alongside other M1c patients with normal LDH. In the selected subgroup, an excess of [redacted] in patients with elevated LDH in the vemurafenib arm is offset by a reduction in other M1c patients of [redacted] resulting in a net imbalance of only [redacted] Performance status showed a similar level of imbalance in the ERG selected subgroup [redacted].

An additional potentially important issue affecting the balance of patient characteristics is evident from Figure 6 of the MS (pg 69) showing BRIM 3[9] patient disposition numbers. Although similar numbers of patients were randomised (337 vemurafenib and 338 dacarbazine), there was a large discrepancy in the number of patients who did not receive the allocated treatment (2 in the vemurafenib arm vs 48 for dacarbazine) dominated by 37 patients who withdrew consent or refused treatment when the allocation to conventional therapy became known. Thus, in practice, the BRIM 3[9] trial went ahead as an unbalanced trial (336 vs 289 patients treated). The size of this discrepancy, amounting to more than 10% of dacarbazine patients, indicates that the relatively small imbalances arising in the ERG selected subgroup may be overshadowed by unknown imbalances in all variables (including stratification variables) in the patients who did not withdraw between randomisation and treatment.

Secondly, it is pointed out by the manufacturer that **imbalances in post-progression treatments received by patients in BRIM 3[9]** in the ERG specified subgroup may confound any results obtained for PPS:

"*In BRIM3 substantially more patients in the dacarbazine arm received systemic post-progression treatment than those in the vemurafenib arm* [redacted]. *Notably, many more* [redacted] *dacarbazine patients than vemurafenib recipients received ipilimumab – the only therapy shown to improve survival in a randomised controlled trial in the second-line setting.*

In addition [redacted] *of dacarbazine patients received an experimental BRAF inhibitor other than vemurafenib or MEK inhibitor (both classes of drug with known activity in BRAF mutant melanoma) compared with* [redacted] *of vemurafenib recipients."*

The ERG is aware of these differences and their potential impact on long-term patient outcomes. Unfortunately, there is no way of eliminating these effects from the trial data based on firm evidence rather than supposition. Nonetheless, the long-term projection of OS rests in large measure on assumptions made about mortality rates beyond confirmed disease progression, and if analysis of data from these patients within the BRIM 3[9] trial is deemed unsafe and unreliable, then the same argument must also apply to the BRIM 3[9] OS patient data and projections obtained from it to make a case for the cost effectiveness of vemurafenib, since the same information is being used to inform model estimates of OS.

6.3 Additional analysis: pre and post progression survival trends

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Post-progression hazards after censoring at the time of crossover (**Error! Reference source not found.**) differ markedly between the two trial arms, with the long-term mortality rate more than [redacted] greater in the vemurafenib arm compared with patients in the dacarbazine arm. This difference is more than sufficient to counter the modest mean PFS gain of [redacted] days, implying an OS advantage in this subgroup in favour of dacarbazine.

The interpretation of these findings is fraught with difficulties which serve only to focus attention on the very great problems involved in obtaining reliable information from clinical trials of treatments for late stage cancer treatments, especially where crucial information can only be obtained from

unconfounded medium and long-term follow-up, but ethical considerations and patient interests dictate short-term trial modification or closure. The data available for the selected subgroup are limited to those patients with the poorest prognosis, whose disease progresses rapidly. In the context of the two-population hypothesis discussed above, it is likely that these patients are predominantly drawn from the 80% expected to progress early and suffer an early death (mean survival less than 12 months). A much longer follow-up would be necessary to obtain sufficient medium term evidence to inform expectations of the long-term benefit of vemurafenib.

The ERG considers that the differences in second-line and subsequent treatments between treatment arms, highlighted by the manufacturer, are likely to be more influential in altering the balance of post-progression mortality risk in favour of dacarbazine than imbalances in baseline characteristics. A tentative conclusion from this analysis is that the available evidence provides no grounds for expecting vemurafenib therapy to be associated with any better PPS than dacarbazine. Therefore, the ERG considers that any projective modelling which results in extended PPS due to vemurafenib is not supported by the BRIM 3 trial[9] results.

7 END OF LIFE

No case has been presented by the manufacturer related to considering the use of vemurafenib under end of life criteria.

8 OVERALL CONCLUSIONS

Trial data provided in the MS demonstrates the efficacy of vemurafenib in terms of OS and PFS in treatment naive patients with locally advanced or metastatic BRAF V600 mutation positive malignant melanoma. The short term nature of the results and the heterogeneity of the patient population impose substantial uncertainty on any projection of the long term benefits. The cost of the intervention and the extended duration of treatment for some patients means that within all considered situations the incremental cost per QALY gained is greater than the accepted willingness-to-pay threshold.

8.1 Implications for research

This population of patients has been disadvantaged with no breakthroughs in treatment in over 30 years. Recent advances are welcome but also raise new research issues including investigation of:

- heterogeneity factors in this patient population
- possible biomarkers that identify patients most likely to benefit from treatment
- possible development of resistance to new treatments
- appropriate second-line treatment.

9 REFERENCES

1. Roche Products Limited. NICE STA submission: vemurafenib for the treatment of locally advanced or metastatic BRAFF V600 mutation positive malignant melanoma 2012.
2. National Institute for Health and Clinical Excellence. Vemurafenib for the treatment of unresectable locally advanced or metastatic BRAFV600 mutation-positive malignant melanoma 2011 [cited 2012 February]; Available from: http://www.nice.org.uk/nicemedia/live/13579/57337/57337.pdf.
3. Xing Y, Chang G, Hu C, Askew R, Ross M, Gershenwald J, *et al.* Conditional survival estimates improve over time for patients with advanced melanoma. Cancer. 2010; 116:2234-41.
4. Dickson R, Boland A, Bagust A, Blundell M, GMassey G, Dundar Y, *et al.* Ipilimumab for previously treated unresectable malignant melanoma: A Single Technology Appraisal. 2011 [cited 2012 February]; Available from: http://www.nice.org.uk/nicemedia/live/12092/56688/56688.pdf.
5. Cancer Research UK. Skin cancer statistics - UK. 2011 [cited 2011 July]; Available from: http://info.cancerresearchuk.org/cancerstats/types/skin/.
6. Balch C, Gershenwald J, Soong S, Thompson J, Atkins M, Byrd D, *et al.* Final version of 2009 AJCC melanoma staging and classification. Journal of Clinical Oncology. 2009; 27:6199-206.
7. Long G, Menzies A, Nagrial A, Haydu L, Hamilton A, Mann G, *et al.* Clinico-pathologic correlates of BRAF mutation status in 207 consecutive patients with metastatic melanoma. Journal of Clinical Oncology. 2010; 28:supp; abstr 8548.
8. Sosman J, Kim K, Schuchter L, Gonzalez R, Pavlick A, Weber J, *et al.* Long-term follow-up of BRAF V600 mutated metastatic melanoma patients treated with vermrafenib reveals prolonged survival. New England Journal of Medicine. 2012; 366:707-14.
9. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. New England Journal of Medicine. 2011; 364:2507-16.
10. National Institute for Health and Clinical Excellence. NICE Guidance on cancer services: Improving outcomes for people with skin tumours including melanoma (update). 2010 [cited 2012 February]; Available from: http://guidance.nice.org.uk/CSGSTIM/Guidance/pdf/English.
11. National Institute for Health and Clinical Excellence. Melanoma (Stage III or IV) - ipilimumab. 2012 [cited 2012 February]; Available from: http://guidance.nice.org.uk/TA/WaveCRS2/48.
12. European Medicines Agency. Europen Medicines Agency recommend approval of first-in-class treatment for metastatic or unresectable melanoma. 2012; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=search.jsp&q=vemurafenib&mid=.
13. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, *et al.* Inhibition of mutated, activated BRAF in metastatic melanoma. New England Journal of Medicine. 2010; 363:809-19.
14. European Medicines Agency. Zelboraf-Summary of Product Characteristics. 2012 [cited 2012 March]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002409/WC500124317.pdf.
15. Roche Products Limited. Statistical Analysis Plan NO25026 (RO5185426)2010.
16. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. BMJ. 2010; 340:c332.
17. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche P, Devereaux P, *et al.* CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trial. BMJ. 2010; 340:c869.
18. Food and Drug Administration. FDA Center for Drug Evaluation and Research Summary Review_Zelboraf. 2011 [cited 2012 February]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202429Orig1s000SumR.pdf.

19. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ. 1999; 319:670-4.
20. Roche Products Limited. Clinical Study Report NO25026-BRIM 32011.
21. Alcala AM, Flaherty KT. BRAF inhibitors for the treatment of metastatic melanoma: clinical trials and mechanisms of resistance. Clinical Cancer Research. 2012; 18:33-9.
22. Poulikakos PI. Acquired resistance to RAF inhibitors is mediated by splicing isoforms of BRAF(V600E) that dimerize in a RAS-independent manner. Molecular Cancer Therapeutics Conference: AACR NCI EORTC International Conference: Molecular Targets and Cancer. 2011; 10.
23. Ribas A, Von Euw E, Attar N, Chu C, Guo D, Lo R, *et al.* Reversal of cross-resistance to BRAF and MEK inhibitors by targeting the AKT/mTOR pathway. Pigment Cell and Melanoma Research. 2010; 23:970.
24. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. 2008; Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
25. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ economic evaluation working party. BMJ. 1996; 313:275-83.
26. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. New England Journal of Medicine. 2011; 364:2517-26.
27. Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos A, Hersey P, *et al.* Societal preference values for advanced melanoma health states in the United Kingdom and Australia. British Journal of Cancer. 2009; 101:387-9.
28. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilites for non small cell lung cancer. Health and Quality of Live Outcomes. 2008; 6:84.
29. National Institute for Health and Clinical Excellence. TA227: erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer. 2011; Available from: http://guidance.nice.org.uk/TA227.
30. National Institute for Health and Clinical Excellence. TA212: Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. 2010; Available from: http://guidance.nice.org.uk/TA212.
31. Fleeman N, Bagust A, Boland A, Dickson R, Dundar Y, Moonan M, *et al.* Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2. Health Technology Assessment. 2011; 15.
32. Hoyle M, Crathorne L, Peters J, Jones-Huges T, Cooper C, Napier M, *et al.* The effectiveness and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with (non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal 118): a systematic review and economic model. 2011; Available from: http://www.nice.org.uk/nicemedia/live/13094/56174/56174.pdf.
33. Hodi F, O'Day S, McDermott D, Weber R, Sosman J, Haanen J, *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. New England Journal of Medicine. 2010; 363:711-23.
34. Miller C, P, Hill M, Pulfer A. A service evaluation to compare secondary care resource use between XELOX and FOLFOX-6 regimes in the treatment of metastic colorectal cancer from a UK National Health Service (NHS) perspective. ISPOR; Athens2008.
35. Joint Formulary Committee. British National Formulary. London 2011; Available from: www.bnf.org.
36. Department of Health. National schedule of reference costs 2009-2010. Department of Health; 2011; Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459.

37. Joint Formulary Committtee. British National Formulary. London 2011; Available from: www.bnf.org.
38. Curtis L. Unit costs of health and social care 2011. 2011 [cited 2012 April]; Available from: http://www.pssru.ac.uk/archive/pdf/uc/uc2011/uc2011.pdf.
39. Sacco JJ, MacBeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: A multicentre retrospective study. PLoS ONE. 2010; 5:e8933.
40. Commercial Medicines Unit - Department of Health. Electronic Market Information Tool (eMit). 2012 [cited 2012 April]; Available from: http://cmu.dh.gov.uk/electronic-market-information-tool-emit/
41. Department of Health. Publications policy and guidance. 2011 [cited 2012 April]; Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459.
42. American Joint Committee on Cancer. Cancer staging. 2009 [cited 2012 April]; Available from: http://www.cancerstaging.org/mission/whatis.html.