NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

STA Submission

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Contents

List of Tables

List of Figures

Abbreviations

AE	Adverse Event
BSC	Best Supportive Care
CEAC	Cost Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CR	Complete Response
CRUK	Cancer Research UK
CSR	Clinical Study Report
EMYY	Embase
EMA	European Medicines Agency
FAS	Full Analysis Set
HR	Hazard Ratio
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention to Treat
KM	Kaplan-Meier
LR*i*G	Liverpool Reviews and Implementation Group
LYG	Life Years Gained
MEIP	Medline in Process
OS	Overall Survival
PD	Progressed Disease
PFS	Progression Free Survival
PR	Partial Response
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RR	Response Rate
SD	Stable Disease
SMC	Scottish Medicines Consortium
TA	Technology Appraisal
TKI	Tyrosine Kinase Inhibitor

Executive summary

Vemurafenib

Vemurafenib (Zelboraf) is an oral tyrosine kinase inhibitor (TKI) of the BRAF serine/threonine kinase. Vemurafenib is the first targeted treatment in melanoma, the first treatment to have demonstrated clinically meaningful survival benefit to be licensed for first line use in melanoma and the first TKI to be approved for use in melanoma.

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 (Long 2010).

Vemurafenib is given as a monotherapy at a dose of 8 x 240 mg tablets per day until disease progression (with the possibility of down-dosing as deemed clinically appropriate in response to toxicity). It is supplied in packs of 56 tablets. The list price of one pack of vemurafenib (7 days supply) is £1,750.

Based upon the phase III clinical trial, it is anticipated that an average course of vemurafenib will cost approximately £[redacted] per patient (see section 6.7)

BRAF V600 Mutation Positive Advanced Melanoma

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, very few

patients (less than 2,000 in the UK) progress to the metastatic stage since most melanomas are diagnosed early and cured by surgery.

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 (Xing 2010).

It is estimated that around 900 patients a year will be eligible to receive vemurafenib in England/Wales. These patients are generally younger than a general melanoma population (a mean age of 50 compared to 60 in BRAF wild-type patients (Long 2010)).

Current UK Clinical Practice

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. In the BRIM3 study approximately 1 in 20 patients experienced a response to treatment with dacarbazine (5.5% response rate). Following relatively rapid progression on first line dacarbazine (median PFS in BRIM3 = 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 mutation testing is not currently undertaken in the NHS. Roche are currently supporting the development of three BRAF testing ‘reference centres’ which will provide the capacity to enable all advanced melanoma patients’ tumours to be tested for *BRAF* mutations.

Efficacy of vemurafenib

Vemurafenib has been studied in one phase 3 RCT (BRIM3) and one phase 2 single arm study (BRIM2).

In BRIM3, vemurafenib was compared to dacarbazine monotherapy in the first line treatment of *BRAF* V600 mutation positive melanoma (n=675). BRIM3 opened for recruitment in January 2010. An interim analysis of the study was conducted in December 2010.

This interim analysis demonstrated a response rate of 48.4% for vemurafenib (compared to 5.5% in the dacarbazine arm), an Overall Survival (OS) Hazard Ratio (HR) of 0.37 and a Progression-Free Survival (PFS) HR of 0.26 ($p<0.001$ for both).

Upon presentation of this data at the ASCO conference in June 2011 and concurrent publication in the *New England Journal of Medicine* vemurafenib was considered as one of the most significant advances in the history of melanoma (a disease area in which the development of effective treatments has been notoriously problematic).

The BRIM2 study (n=132) is a single arm study designed to investigate the efficacy of vemurafenib in the treatment of previously treated *BRAF* V600 mutation positive melanoma patients. The latest analysis of BRIM2 demonstrates a response rate of 53% (nearly 10 times that observed for dacarbazine in BRIM3) and a median overall survival estimate of 15.9 months.

Following the release of the BRIM3 data vemurafenib received one of the most rapid FDA approvals in history (with less than 18 months from the first patient entering BRIM3 in January 2010 to vemurafenib being available in the USA). In December 2011 the CHMP similarly granted vemurafenib a positive opinion for use in BRAF V600 mutation positive advanced melanoma, after an accelerated review process. It is anticipated that this opinion will be converted to an EMA marketing authorisation in February 2012.

The anticipated role of vemurafenib in English/Welsh clinical practice

It is anticipated that if vemurafenib were to be NICE endorsed, *BRAF* mutation testing of all advanced melanoma patients would become standard clinical practice and that the majority of patients found to be BRAF V600 mutation positive would receive vemurafenib as a first line treatment.

In order to facilitate patient access to vemurafenib in the period following the presentation of the BRIM3 data (and broaden its safety database) Roche has offered vemurafenib under an expanded access program since June 2011. There are now 12 UK centres offering this trial. In the 6 months since the first centre opened almost 200 UK patients have been recruited (during this period only about 450 new cases of inoperable *BRAF* mutation-positive melanoma would be expected to present in the UK). The success of this expanded access program demonstrates the significant unmet need for this population and the enthusiasm of clinicians and patients to be able to access vemurafenib.

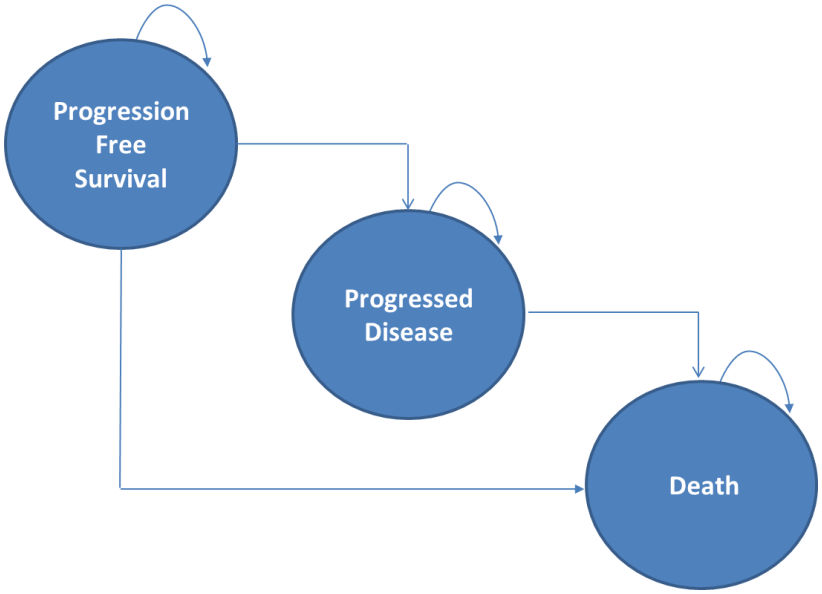
Cost-effectiveness

Previously untreated patients

A 3 state partitioned survival model (Progression Free Survival, Progressed Disease and Death) was developed in order to investigate the cost-effectiveness of vemurafenib compared to dacarbazine in the first line treatment of BRAF V600 mutation positive melanoma.

The model employed an England/Wales NHS PSS perspective, non-differential discounting at 3.5% per annum, a one week cycle length and a half-cycle correction where appropriate. A time horizon of 30 years was used in the base-case (equivalent to a life-time time horizon).

Figure 1: Model Structure

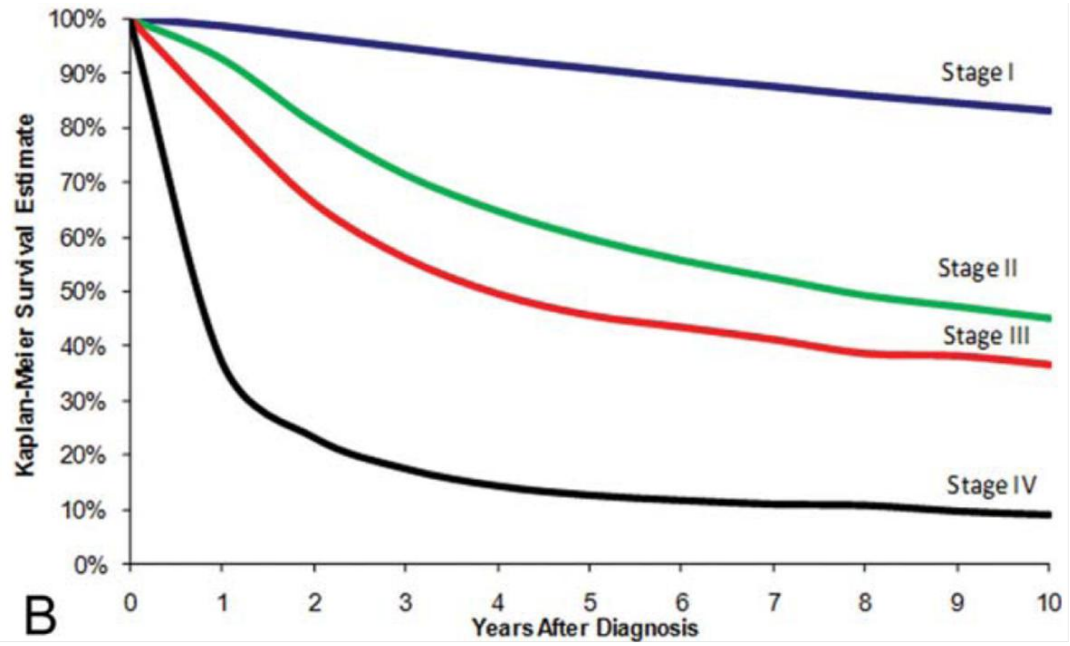


The model incorporates a wide range of costs based upon BNF62, NHS reference costs and previous NICE appraisals including the cost of vemurafenib, the cost of dacarbazine, the cost of drug administration, pharmacy costs, AE costs, best supportive care costs, cost of palliative/end of life care and the cost of BRAF testing. Utilities were taken from Beusterien et al and include weighting by response rates in order to capture the difference in quality of life associated with achieving a response to treatment compared to disease stabilisation.

As a large element of BRIM3 patients have yet to experience an event, it was necessary to apply extrapolation to the data observed in order to estimate long term outcomes for vemurafenib and dacarbazine patients. For dacarbazine this was done utilising a synthesis of BRIM3, the control arm from the 'Robert' study and data from the 'SEER' registry. Whilst extrapolation in NICE oncology appraisal is commonly done by simply extrapolating the data observed using a single parametric function in the case of advanced melanoma this appears inappropriate

The survival curves for Stage IV advanced melanoma patients from the SEER registry are presented below (featuring over 1,000 stage IV patients).

Figure 2: The SEER registry data



This registry data demonstrates that whilst around 80% of patients have died within 2 years of diagnosis approximately 9.1% of these patients are still alive at 10 years following diagnosis (Xing 2010). It is potentially important to consider this heterogeneity in expected survival when modelling as failure to do so may result in extrapolation that has poor face-validity when compared to historical data.

Due to the immaturity of the BRIM3 data and the hazard trends observed in other data in melanoma this ‘synthesis’ approach was used in order to ensure the model accurately reflected historical data in advanced melanoma.

In the base-case the dacarbazine arm was modelled utilising a combination of BRIM3, the control arm from the Robert study and a long-term hazard which resulted in 9.1% of patients being alive 10 years after commencing treatment (as per the SEER registry). A vemurafenib arm was then simulated using the BRIM3 data on the assumption that vemurafenib provided no further treatment effect from month 14

onwards (potentially conservative given the length of time some patients remain on vemurafenib for). The results of this base case analysis are presented in Table 1.

Table 1 Base-case cost-effectiveness results- previously untreated patients

	Vemurafenib	Dacarbazine
Technology acquisition cost	[redacted]	[redacted]
Other costs*	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Difference in total costs	[redacted]	
LYG	[redacted]	[redacted]
LYG difference	[redacted]	
Cost per life year gained	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	
ICER	£94,267	

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

*Best supportive care, administration costs, pharmacy costs etc

A range of alternative OS extrapolation methods were tested in sensitivity analysis. In each of these the ICER remained above £75,000/QALY gained. The ICER estimated was most sensitive to extrapolation of overall survival and the discount rate applied for health outcomes (removing discounting of health dropped the ICER to £70,358). PSA demonstrates vemurafenib has a very low probability of being cost-effective up to a threshold of around £90,000/QALY gained.

The immaturity of the BRIM3 data, and the sensitivity of the ICER to the extrapolation employed mean that there is significant uncertainty around the magnitude of the ICERs estimated. However, based on the best current evidence it appears most likely that the ICER associated with use of vemurafenib in a first line setting is above the range typically considered acceptable in NICE appraisals.

Previously treated patients

Due to the ICERs estimated in the first-line setting and the uncertainty associated with those ICERs (despite the availability of randomized data compared to the treatment of interest), compounded in the second-line setting by the lack of control arm in the BRIM2 study and the lack of historical control data on the outcomes experienced by previously treated *BRAF* V600 mutated patients, it is not possible to robustly demonstrate that vemurafenib is a cost-effective use of NHS resources in the second line treatment of advanced melanoma.

Given this a *de novo* model has not been constructed in this setting.

Budget Impact

The budget impact of NICE approval of vemurafenib would be as shown in Table 2 below. The assumptions underlying these figures are provided in Section 7.

Table 2: Budget impact by year

Year	1	2	3	4	5
Budget Impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Zelboraf (vemurafenib) is a small molecule antineoplastic agent that selectively inhibits oncogenic BRAF serine-threonine kinases.
ATC code: L01XE15 (temporary ATC code)

1.2 What is the principal mechanism of action of the technology?

Vemurafenib selectively inhibits the mutated BRAF enzyme that is found in around half of malignant melanomas where it drives abnormal proliferation and promotes cell survival. Inhibition removes a key growth driver and restores normal apoptotic processes resulting in selective tumour cell death and tumour shrinkage.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

On May 4, 2011, a request for Marketing Authorization for vemurafenib was submitted to the European Medicines Agency. A positive CHMP opinion was received in December 2011 and it is anticipated that this opinion will be converted to a marketing authorization in February 2012.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the

marketing authorisation (for example, exceptional circumstances/conditions to the licence).

We are currently unaware of any issues raised by the EMA and do not yet have access to an EPAR.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

It is anticipated that vemurafenib will be indicated 'for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma'.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Phase 3 Studies

There is currently one ongoing phase 3 RCT investigating vemurafenib for the treatment of BRAF V600 mutation-positive metastatic melanoma; the 'BRIM3' study.

BRIM3 is a multi-national RCT in which vemurafenib monotherapy is being compared to dacarbazine monotherapy (DTIC) in the first line treatment of BRAF mutation-positive metastatic melanoma patients (n = 675).

The interim analysis of the BRIM3 study was published in the New England Journal of Medicine (NEJM) in June 2011 (Chapman et al 2011). In this publication the use of vemurafenib rather than DTIC was associated with a 74% reduction in the risk of disease progression (PFS HR = 0.26 {0.20, 0.33}) and a 63% reduction in the risk of death (OS HR = 0.37 {0.26, 0.55}).

The BRIM3 study is still ongoing (albeit with a recommendation from the independent data and safety monitoring board that crossover to vemurafenib be recommended) and more mature data from the study will continue to be made available over time.

It is anticipated that an updated analysis of the BRIM3 data will be made in February 2012. Following data cleaning the results of this cut should be available at around the time of consultation on the ACD (the second quarter of 2012).

Phase 2 Studies

BRIM2 is a single-arm, open-label, multinational phase 2 study in which vemurafenib monotherapy is being studied in patients who have previously received treatment for their metastatic melanoma (n=132). Data from BRIM2 has been previously presented at the Annual Conference of the American Society of Clinical Oncologists (ASCO) in June 2011 (Ribas 2011). It is anticipated that new data from the BRIM2 study will be made available in the first quarter of 2012.

Various other phase 2 studies investigating vemurafenib are ongoing. As these studies are still recruiting the date of availability of results in uncertain.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

On May 4, 2011, a request for Marketing Authorization for vemurafenib was submitted to the European Medicines Agency. A positive CHMP opinion was received in December 2011. Vemurafenib will be launched as soon as this CHMP opinion is converted to an EMA marketing authorization (within 67 days after the opinion is issued).

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Zelboraf received FDA approval on August 17, 2011 with the following indication: *'Zelboraf is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test'.*

On October 19, 2011 Zelboraf was approved in Switzerland. The approved indication is for the treatment of unresectable or metastatic melanoma patients with a BRAF V600 mutation.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

A submission will be made to the Scottish Medicines Consortium (SMC) on the 5th March 2012. It is anticipated that the SMC will make their decision public on the 9th July 2011.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1 Unit costs of technology being appraised

<table>
<tr><td>Pharmaceutical formulation</td><td>Film-coated tablet. Pinkish white to orange white, oval, biconvex film-coated tablets, with VEM engraved on one side.</td></tr>
<tr><td>Acquisition cost (excluding VAT)</td><td>Vemurafenib will be sold at a price of £1,750 for one pack of 56 x 240 mg tablets.</td></tr>
<tr><td>Method of administration</td><td>Vemurafenib tablets are to be swallowed whole with water. Vemurafenib tablets should not be chewed or crushed.</td></tr>
<tr><td>Doses</td><td>The recommended starting dose of vemurafenib is 960 mg (4 tablets of 240 mg) twice daily (equivalent to a total daily dose of 1,920 mg).

The first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. Vemurafenib is to be taken either one hour before or two hours after each meal (morning/evening).</td></tr>
<tr><td>Dosing frequency</td><td>8 x 240 mg vemurafenib tablets should be taken daily (4 in the morning and 4 in the evening) until disease progression or unacceptable toxicity.</td></tr>
<tr><td>Average length of a course of treatment</td><td>Mean progression free survival (with extrapolation) for a vemurafenib randomised patient in BRIM3 is estimated at approximately 7 months. As treatment is given until disease progression an average course of treatment will be expected to last for 7 months.</td></tr>
<tr><td>Average cost of a course of treatment</td><td>In economic modelling an expected cost of £[redacted] per patient was estimated.</td></tr>
<tr><td>Anticipated average interval between courses of treatments</td><td>Only one course of vemurafenib will be taken by a patient (treatment is continuous until disease progression when it is stopped).</td></tr>
<tr><td>Anticipated number of repeat courses of treatments</td><td>Only one course of vemurafenib will be taken by a patient.</td></tr>
<tr><td>Dose adjustments</td><td>Management of adverse drug reactions may require dose reduction, temporary interruption and/or treatment discontinuation (see table 1). Posology adjustment resulting in a dose below 480 mg twice daily are not recommended. Note that reduced doses are achieved using multiples of 240 mg tablets. No resupply is required at dose reduction and wastage is thus minimized.

Table 1: Dose modification schedule
<table>
<tr><th>Grade (CTC-AE)*</th><th>Recommended Dose Modification</th></tr>
<tr><td>Grade 1 or Grade 2 (tolerable)</td><td>Maintain vemurafenib at a dose of 960 mg
twice daily</td></tr>
</table>
</td></tr>
</table>

	Grade 2 (intolerable) or Grade 3	
	1st Appearance	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily.
	2nd Appearance	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily
	3rd Appearance	Discontinue permanently
	Grade 4	
	1st Appearance	Discontinue permanently or interrupt vemurafenib treatment until grade 0 – 1. Resume dosing at 480 mg twice daily
	2nd Appearance	Discontinue permanently
	*The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE).	

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Vemurafenib is a targeted therapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. The use of vemurafenib in the NHS would therefore require that metastatic melanoma patients' tumours are tested for the presence or absence of a BRAF V600 mutation. Those patients whose tumours are found to harbour a BRAF V600 mutation will be eligible to receive vemurafenib whilst those patients whose tumours are found not to harbour a BRAF V600 mutation will continue to receive standard treatment.

BRAF mutations are found in approximately 50% of melanomas (Long et al 2011).

A companion diagnostic test (cobas® 4800 BRAF V600 Mutation Test) has been developed in order to identify metastatic melanoma patients with a BRAF V600 mutation who may benefit from vemurafenib therapy, though other testing technologies are available.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

The use of vemurafenib is associated with no additional monitoring resource requirement beyond usual clinical practice. Whilst there may be an increased focus on monitoring patients' skin for the development cuSCCs when using vemurafenib (one of the AEs associated with inhibition of BRAF) this is unlikely to require significant additional monitoring resource. The cost of treating these cuSCCs and other associated AEs (i.e. keratocanothoma) will be considered in the economic evaluation undertaken,

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Vemurafenib is given as a monotherapy and so no significantly costly or burdensome treatments are administered alongside it. It is possible that a patient will require supportive medications to prevent manage treatment side-effects (see Section 2.7).

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Malignant melanoma is a tumour that arises from melanocytic cells and primarily involves the skin. Tumours may arise de novo or from pre-existing skin naevi (moles). Individuals with large numbers of common naevi and those with congenital naevi, multiple naevi, and/or atypical naevi (dysplastic naevi) are at greater risk. The inheritance of melanoma is polygenic, with 5 to 10% of melanomas appearing in melanoma-prone families. In addition to these genetic and constitutional factors, the most important exogenous factor is exposure to UV irradiation, particularly intermittent sun exposure.

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%.

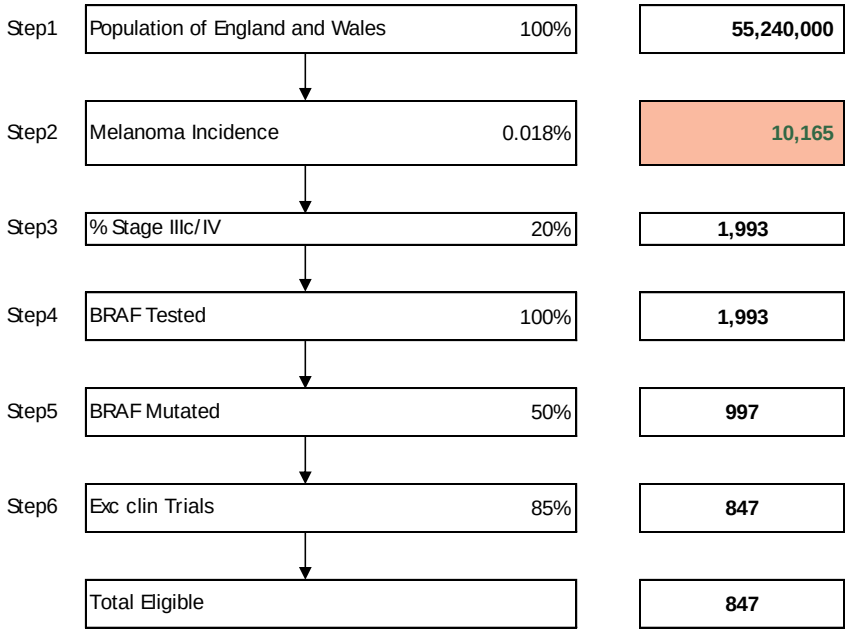
Around 10% of patients have metastatic disease at diagnosis or relapse with metastatic spread after treatment for apparently localised disease. Survival for patients with metastatic disease is very poor with 5 year survival of 7-20% for stage IV disease (NICE, Vemurafenib Final Scope). Patients with uncontrolled (i.e. progressive) metastatic disease are generally very symptomatic with a consequently low quality of life. UK clinicians report that in patients who experience tumour shrinkage on vemurafenib symptoms can be rapidly and dramatically reduced with a resultant positive impact on quality of life of a magnitude that is rare with conventional chemotherapy

2.2 How many patients are assumed to be eligible? How is this figure derived?

It is estimated that approximately 850 patients per annum will be eligible to receive vemurafenib for BRAF mutation-positive unresectable or metastatic melanoma.

The derivation of this number is provided in figure 1 below:

Figure 3. Eligible Patient Population Algorithm



Reference

1. http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/mid-2010-population-estimates/index.html

2. Roche Data on File: RXUKDONF00025 (includes Methodology for calculating Cathcment area population derived incidence)

3. Internal Estimate (Includes progressed from early stages)

4. Internal estimate: Assumption is that all patients that are treated with sytemic treatment are tested

4. Long GV et al, 2010

5. Internal Estimate; based on Patient Allocation Research

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Guidelines

In 2006 NICE published guidance on the development of cancer services for people with skin tumour including melanoma (http://www.nice.org.uk/CSGSTIM).

This document focused on the organisation of services. It pre-dated the emergence of vemurafenib. Non-surgical treatment options included dacarbazine, interferon-alpha and immunotherapy.

Technology Appraisals

There is currently an ongoing STA assessing the use of ipilimumab (Yervoy) in the second line treatment of metastatic melanoma. This is the first NICE technology appraisal in melanoma and is currently due to result in guidance in February 2012.

No subgroups were addressed in the above guideline/appraisal.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Currently it is standard clinical practice to give previously untreated metastatic melanoma patients dacarbazine (DTIC) as a first line treatment. Following disease progression a patient will then receive best-supportive care alone, ipilimumab (if located in one of the regions in which ipilimumab is available

through the Cancer Drugs Fund) or, potentially, be entered into a clinical trial of an investigational agent. If ipilimumab were to be NICE recommended as a second line treatment option in the ongoing STA then it, rather than best supportive care, would become the standard of care in all regions rather than in solely those regions in which it is available on the Cancer Drugs Fund.

Given the relative paucity of effective treatment options in melanoma and the significant advances currently being achieved and anticipated in the near future (via the development of immunotherapies, BRAF targeted therapies, MEK inhibitors and combinations therapies) trial participation in melanoma is relatively common.

If vemurafenib were to be NICE approved this pathway would change in two ways.

1) Testing for BRAF mutations would become standard clinical practice

2) Those patients found to have tumours which are BRAF mutation-positive would receive vemurafenib as first line therapy. The treatment of patients with BRAF mutation-negative metastatic melanoma would remain unchanged. Note that although it is anticipated that vemurafenib will be licensed for both first- and second-line use, Roche believes that, given the opportunity, clinicians will opt to use it first-line in preference to dacarbazine. This is because vemurafenib has been shown in a phase III study to produce outcomes far superior to dacarbazine, a treatment which, although the “standard treatment” in clinical trials is widely regarded as offering only very limited efficacy. It has never been shown in a randomised clinical trial to improve overall or progression-free survival and induces tumour shrinkage in only about 5.5% of patients (BRIM3 control arm)

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

The key uncertainty in terms of the economic evaluation undertaken is whether or not ipilimumab should be considered as a second-line treatment or whether BSC alone should be modelled. As the ICERs associated with ipilimumab in its on-going STA are extremely uncertain and significantly higher than the commonly used thresholds (in even the most optimistic scenarios – i.e. the manufacturer of ipilimumab assumed that after 5 years in the model patients were 'cured' of their metastatic melanoma without any evidence to support this claim) in the modelling undertaken it was assumed that ipilimumab would not be recommended by NICE and that BSC would be the most appropriate second line treatment for inclusion in the vemurafenib model. If ipilimumab is approved during the course of this appraisal this may warrant modifications to the economic evaluation undertaken.

2.6 Please identify the main comparator(s) and justify their selection.

As defined in the scope the main comparators to vemurafenib are dacarbazine in the first line setting and best-supportive care or ipilimumab (if NICE approved) in the second line setting. Although its efficacy is not impressive, dacarbazine has been the standard first-line treatment for inoperable melanoma for three decades and has been control treatment in numerous Phase III trials which have, until recently failed to identify more effective treatments. Ipilimumab is the first treatment shown to have meaningful benefit as a second-line treatment in a controlled trial and in its absence, second-line treatment is often not offered in the UK and when it is no standard treatment can be said to exist.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The main events and treatments that may be given, should the events become intolerable, include:

- Arthralgia – simple analgesia, steroids

- Photosensitivity – sun-screen creams
- Rash – ointments, steroids
- Pruritus – anti-histamines
- Nausea – anti-emetics
- Cutaneous squamous cells carcinomas – treated by excision conducted as an outpatient procedure under local anaesthetic

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Being a twice daily oral therapy, this treatment will be self-administered by patients at home.

Benefits relative to dacarbazine treatment include reduced chair time in the chemotherapy unit, pharmacy time in reconstituting IV cytotoxic therapy, liberating capacity for other treatment infusions.

Histopathology services are required to test for the BRAF mutation on tumour excision or biopsy samples. However this testing is being provided free of charge by Roche until further notice to hospitals who do not wish to or do not have capacity to conduct their own testing.

2.9 Does the technology require additional infrastructure to be put in place?

Beyond the requirement to facilitate BRAF testing we do not anticipate that the use of vemurafenib will require additional infrastructure to be put in place.

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

To our knowledge there are no such issues identified in NICE guidance or protocols in metastatic melanoma.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

None.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

N/A.

4 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	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.	As per scope.	N/A

	Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	None	As per scope.	N/A
Special considerations, including issues related to equity or equality	None	As per scope.	N/A

Section B – Clinical and cost effectiveness

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)		

5 Clinical evidence

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

Medline (MEYY), Embase (EMYY), Medline in Process (MEIP) and the Cochrane Library were searched for randomised evidence on the efficacy of vemurafenib (also known as RO5185426 or PLX4032) in the treatment of melanoma in patients with mutations of the BRAF gene. MEYY, EMYY and MEIP were searched using Dialogue DataStar whilst the Cochrane Library was searched via the Cochrane Library website. The search strategies used are provided in section 9.2, appendix 2. In addition to these databases internal experts on the clinical trial program for vemurafenib were consulted in order to ensure all relevant studies were identified.

Each database was searched individually for potentially relevant records. The duplicates from these records were then removed and the remaining individual studies' titles/abstracts assessed against the pre-defined inclusion/exclusion criteria by a single reviewer (see section 5.2.1.). Where a record was found to be irrelevant the reason for its exclusion was detailed. Where a record was identified as being potentially relevant based upon the title/abstract it was retrieved in full for an assessment against the inclusion/exclusion criteria.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

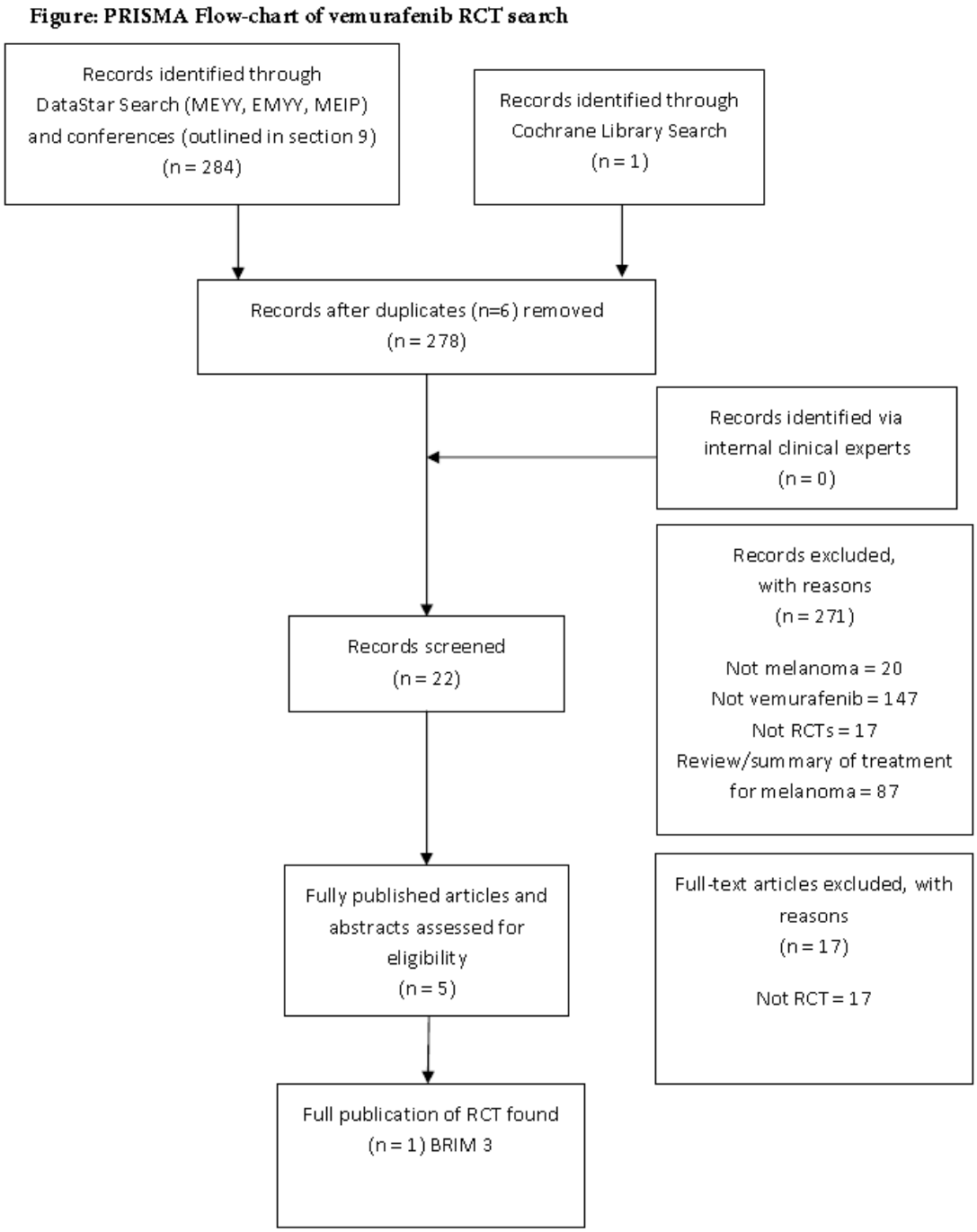
Table 3: Eligibility criteria used in search strategy

	Inclusion Criteria	Exclusion Criteria
Population	Previously untreated unresectable or metastatic melanoma patients with BRAF V600 mutation-positive	Patients with non-metastatic or resectable melanoma, with BRAF mutation negative status or not selected on basis of BRAF mutation status
Interventions	Vemurafenib monotherapy	Non-vemurafenib therapy
Comparators	Accepted drug therapy standard of care : Dacarbazine (also known by the brand name, DTIC) therapy	-
Outcomes	Progression Free Survival, Overall Survival, Adverse Events	-
Study Design	Randomised controlled trials	Observational data, registry analyses, single arm studies, meta-analyses

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-

statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

Figure 4: PRISMA Flow-chart of vemurafenib RCT search



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

One RCT was identified, based upon a single full publication of the phase 3 data for vemurafenib in the treatment of metastatic melanoma:

Chapman PB et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. N Engl J Med 2011;364:2507-2516).

This study, known by the acronym BRIM 3, has the ClinicalTrials.gov Identifier, NCT01006980 and Roche trial no. NO25026.

It had also been presented at international congresses, with accompanying abstract publications, as follows:

1. Chapman, P et al. Phase III randomized, open-label, multi-centre trial (BRIM3) comparing BRAF inhibitor vemurafenib with dacarbazine in patients with BRAFV600E-mutated melanoma (Abstract #LBA4). Presented at ASCO 2011 (Podium).

2. McArthur GA et al. Vemurafenib improves overall survival compared to dacarbazine in advanced BRAFV600E-mutated melanoma: Updated survival results from a Phase III randomised, open-label, multicentre trial (Abstract #28LBA). Presented at ECCO/ESMO 2011(Podium).

Finally some data has been taken from the draft Zelboraf (vemurafenib) Summary of Product Characteristics (December 2011).

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches

conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Study title:

BRIM 3: A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving RO5185426 or Dacarbazine

Table 4: List of relevant RCTs for vemurafenib

ClinicalTrials.gov Identifier: NCT01006980 Roche trial no. NO25026 (BRIM 3)			
Intervention	**Comparator**	**Population**	**Primary study ref.**
Vemurafenib 960 mg twice daily orally	Dacarbazine 1000 mg per square meter of body-surface area by intravenous infusion on day 1 every 3 weeks (3 week cycle)	Previously untreated BRAF mutation-positive metastatic melanoma patients	See 5.2.3

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The RCT identified was the BRIM 3 study. See 5.2.3.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the

rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Not applicable.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

A single non-RCT study supports the evidence for the efficacy of vemurafenib in previously treated patients with BRAF V600 mutation-positive unresectable or metastatic melanoma - BRIM 2, a single arm, open-label phase 2 study (Ribas A et al. BRIM 2: An open-label, multicentre phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma. J Clin Oncol 29: 2011 (suppl; abstr 8509)).

Table 5: List of relevant non-RCTs for vemurafenib

ClinicalTrials.gov Identifier: NCT00949702 Roche trial no. NP22657 (BRIM-2)				
Intervention	**Population**	**Objectives**	**Primary study ref.**	**Justification for inclusion**
Vemurafenib	Previously treated BRAF mutation-positive metastatic melanoma patients	To confirm the ORR and anti-tumour activity of vemurafenib in previously treated patients with BRAFV600-mutated melanoma	Ribas A et al. BRIM 2: An open-label, multicentre phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma. J Clin Oncol 29: 2011 (suppl; abstr 8509); Sosman JA et al. Long-term follow-up of BRAFV600mutated metastatic melanoma patients treated with vemurafenib reveals prolonged survival. NEJM 2012.	Provides data on tolerability, safety and efficacy in previously treated metastatic melanoma patients.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

The regulatory submission which formed the basis of the FDA's and EMA's regulatory approval for vemurafenib as 1st line treatment for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma was based primarily on the BRIM 3 study.

The Data Safety Monitoring Board (DSMB) for BRIM 3 recommended release of the results of this study, due to compelling efficacy based on review of the

results of the planned interim analysis of OS presented on January 14, 2011. The final PFS analysis was reviewed by the DSMB at that time.

Subsequent to the January 2011 DSMB meeting, data collection and cleaning were completed for the purpose of the CSR. The final database for the purpose of the CSR was obtained on February 7, 2011, with updated adverse event and laboratory data obtained on February 28 and April 1, 2011, respectively. All data presented and published by Chapman et al (NEJM, 2011) was taken from analysis of data evaluated by the clinical cut-off date of December 30, 2010.

The data set from December 2010 was used for the US regulatory submission. This data set was sufficient to provide support to meet one of the co-primary endpoints i.e. progression-free survival. However the duration of follow-up was limited when compared to other studies and not sufficient to provide data for survival analysis. Therefore two further data sets (at the time of production of this submission) were required to demonstrate the survival benefit conferred by vemurafenib, produced in March 2011 and October 2011.

Therefore data set from BRIM 3 has been and continues to be updated since the study subjects are still under follow-up. The most recent survival data will be included, based on the most recent data cut (October 2011) which is to be included in the Summary of Product Characteristics.

At the time of the interim analysis of BRIM 3, the subjects receiving dacarbazine were offered the option of crossing over to receive vemurafenib instead in view of the improved efficacy and acceptable safety profile. These patients were censored in subsequent analyses. At the time of the data set from October 2011, 81 patients (24%) who had been receiving dacarabzine had crossed over to the vemurafenib arm.

The data from BRIM-2 is due to be published in early 2011. These data are included to ensure that the appraisal has the benefit of the most recent available information.

Supportive evidence for the efficacy of vemurafenib in previously treated patients with BRAF V600 mutation-positive unresectable or metastatic melanoma has been taken from BRIM 2.

Methods

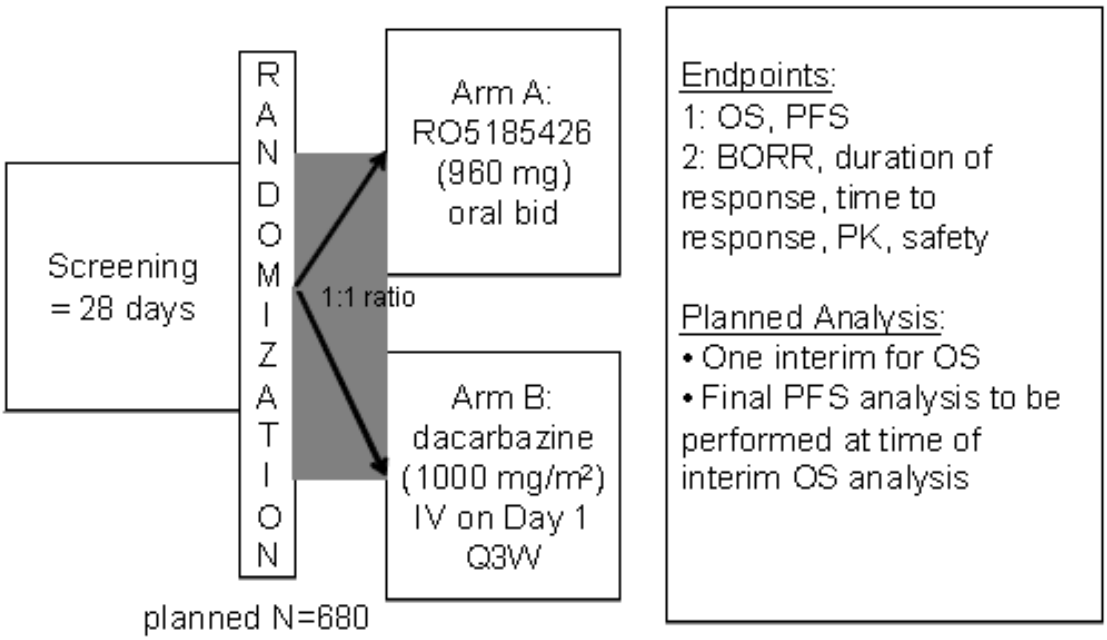
5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table 6: Comparative summary of methodology of BRIM 3

Trial no. **(acronym)**	**ClinicalTrials.gov Identifier: NCT01006980.** **Roche trial no. NO25026** **(BRIM 3)**
Location	International, multi-centre (Western Europe, North America, Australia/New Zealand, and Israel)
Design	Randomized, open-label, active-treatment controlled, multicentre, Phase 3 study. The study design for BRIM 3 is illustrated in Figure 5 (below this table).
Duration of study	January 4, 2010 (first patient randomized) to December 30, 2010 (clinical cut-off date for Final Analysis of PFS leading to patient cross-over). Follow-up continues
Method of randomisation	Randomization was performed by Almac Clinical Technologies, Yardley, PA, using an interactive voice recognition system (IVRS) in 1:1 ratio to receive either vemurafenib (at a dose of 960 mg twice daily orally) or dacarbazine (at a dose of 1000 mg per square meter of body-surface area by intravenous infusion every 3 weeks). Baseline characteristics of the patients were well balanced. Study patients were stratified according to American Joint Committee on Cancer stage (IIIC, M1a, M1b, or M1c), ECOG performance status (0 or 1), geographic region (North America, Western Europe, Australia or New Zealand, or other region), and serum lactate dehydrogenase level (normal or elevated).
Method of blinding (care provider, patient and outcome assessor)	The study was conducted in an open-label manner. However, the allocation of treatments during the randomisation process was concealed via an interactive voice recognition system (IVRS), performed by Almac Clinical Technologies.
Intervention(s) (n =) and	Vemurafenib 960 mg twice daily orally (n = 337)

comparator(s) (n =)	Dacarbazine 1000 mg per square metre of body-surface area by intravenous infusion on day 1 every 3 weeks (3 week cycle) (n = 338)
Primary outcomes (including scoring methods and timings of assessments)	Rates of overall survival and progression-free survival See Table 9, Table 13.
Secondary outcomes (including scoring methods and timings of assessments)	These included assessment of the efficacy of vemurafenib using confirmed best overall response rate (BORR), duration of response, and time to response. See Table 9, Table 13. Other outcomes included (see Table 9): • To evaluate the tolerability and safety profile of vemurafenib. • To further characterize the pharmacokinetic (PK) profile of vemurafenib • To contribute to the validation of the cobas® 4800 BRAF V600 Mutation Test. • Exploratory objectives: See Table 9.
Duration of follow-up	Median follow-up for the interim analysis was 3.8 months for patients in the vemurafenib group and 2.3 months for those in the dacarbazine group. Follow-up is on-going

Figure 5: BRIM 3 Study Design and Endpoint Summary



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

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table 7: Eligibility criteria in BRIM 3

ClinicalTrials.gov Identifier: NCT01006980. **Roche trial no. NO25026 (BRIM 3)** ***(Clinical Study Report – NO25026 –BRIM 3. Research Report Number 1039652. April, 2011)***	
Inclusion criteria	**Exclusion criteria**
Patients had to meet all of the following criteria to be included in the study: 1. Male or female patients ≥ 18 years of age 2. Histologically confirmed metastatic melanoma (surgically incurable and unresectable Stage IIIC or Stage IV (American Joint Committee on Cancer [AJCC]). Unresectable Stage IIIC disease needed confirmation from a surgical oncologist. 3. Treatment-naïve, i.e., no prior systemic anti-cancer therapy for advanced disease (Stage IIIC and IV). Only prior adjuvant immunotherapy was allowed. 4. Must have had a BRAFV600-positive mutation (by Roche cobas test) prior to administration of study treatment 5. ECOG performance status of 0 or 1 6. Life expectancy > 3 months 7. Measurable disease by RECIST criteria (version 1.1) prior to the administration of study treatment 8. Must have recovered from effects of any major surgery or significant traumatic injury at least 14 days before	Patients meeting any of the following criteria were excluded from the study: 1. Any active central nervous system (CNS) lesion (i.e., those with radiographically unstable, symptomatic lesions). However, patients treated with stereotactic therapy or surgeries were eligible if patient remained without evidence of disease progression in brain ≥ 3 months. Patients were also required to be off corticosteroid therapy for ≥ 3 weeks. Whole brain radiotherapy was not allowed with the exception of patients who had definitive resection or stereotactic therapy of all radiologically detectable parenchymal lesions. 2. History of carcinomatous meningitis 3. Regional limb infusion or perfusion therapy 4. Anticipated or on-going administration of anti-cancer therapies other than those administered in this study 5. Pregnant or lactating women 6. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant

the first dose of study treatment 9. Cutaneous SCC lesions identified at baseline must be excised. Adequate wound healing was required prior to study entry. Baseline skin exam was required for all patients. 10. Adequate haematologic, renal, and liver function as defined by laboratory values performed within 28 days prior to initiation of dosing: • Absolute neutrophil count (ANC) ≥ 1.5 x 109/L • Platelet count ≥ 100 x 109/L • Haemoglobin ≥ 9 g/dL • Serum creatinine ≤ 1.5 x upper limit of normal (ULN) • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN • Bilirubin ≤ 1.5 x ULN (for patients with Gilbert's Syndrome, bilirubin ≤ 3 x ULN) • Alkaline phosphatase ≤ 2.5 x ULN (≤ 5 x ULN for patients with concurrent liver metastases) 11. For pre-menopausal women, negative serum pregnancy test within 10 days prior to commencement of dosing; women of non-childbearing potential were included if they were either surgically sterile or postmenopausal for ≥ 1 year	small bowel resection that would preclude adequate vemurafenib absorption (patients had to be able to swallow pills) 7. Mean QTc interval ≥ 450 msec at screening 8. NCI CTCAE Version 4.0 grade 3 haemorrhage within 4 weeks of starting the study treatment 9. Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, serious cardiac arrhythmia requiring medication, uncontrolled hypertension, cerebrovascular accident or transient ischemic attack, or symptomatic pulmonary embolism 10. Known clinically significant active infection 11. History of allogeneic bone marrow transplantation or organ transplantation 12. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with study participation or study drug administration, or could interfere with the interpretation of study results, which in the judgment of the investigator would make the patient inappropriate for entry

12. For fertile men and women, the use of an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician, in accordance with local requirements 13. Absence of any psychological, familial, sociological or geographical condition that would potentially hamper compliance with the study protocol and follow-up schedule; such conditions were discussed with the patient before trial entry 14. A signed informed consent form (ICF) obtained prior to study entry and prior to performing any study-related procedures	into this study 13. Previous malignancy within the past 5 years, except for basal or squamous cell carcinoma of the skin, melanoma in-situ, and carcinoma in-situ of the cervix (an isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer was allowed) 14. Previous treatment with a BRAF inhibitor 15. Known human immunodeficiency virus (HIV) positivity, AIDS-related illness, active hepatitis B virus, or active hepatitis C virus 16. Randomization to this trial at another participating site

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table 8: Baseline characteristics of patients in BRIM 3

Trial no. **ClinicalTrials.gov Identifier: NCT01006980.** **Roche trial no. NO25026** **(BRIM 3)** **Baseline characteristic**	**Vemurafenib**	**Dacarbazine**
(n = 675)	**(n = 337)**	**(n = 338)**
Median age (range) — yr (%)	56 (21–86)	52 (17–86)
Gender	200 (59)	181 (54)
White race — no. (%) - self-reported	333(99)	338 (100)
Geographic region — no. (%)		
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 performance status — no. (%)		
0	229 (68)	230 (68)
1	108 (32)	108 (32)
Extent of metastatic melanoma — no. (%)		
M1c	221 (66)	220 (65)
M1b	62 (18)	65 (19)
M1a	34 (10)	40 (12)
Unresectable IIIC	20 (6)	13 (4)
Lactate dehydrogenase — no. (%)		
≤Upper limit of the normal range	142 (42)	142 (42)
>Upper limit of the normal range	195 (58)	196 (58)
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table 9: Primary and secondary outcomes of the BRIM 3

ClinicalTrials.gov identifier: NCT01006980 **Roche trial no. NO25026** **(BRIM 3)**	**Outcomes**	**Reliability/validity/ current use in clinical practice**

Primary outcome(s) and measures	**Overall Survival** OS was defined as the time from randomization 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. The last date the patient was known to be alive was derived as the latest date of contact or study assessment. Survival time for patients with no post-baseline survival information was censored on the date of randomization. The primary analysis of OS was a comparison of the two treatment groups using an unstratified log-rank test (two-sided). The hazard ratio for death for vemurafenib relative to dacarbazine and the associated 95% CI were computed using a Cox regression model. Median OS was estimated using the Kaplan-Meier method, with 95% CI calculated using the method of Brookmeyer et al (1982). The plot of Kaplan-Meier estimate of OS for each treatment group for the interim analysis (including associated 95% CI) and for the updated analysis (see Figure 3Figure 12) are provided. Median OS is also provided. **Progression-Free Survival**	These outcomes and measures are commonly accepted and currently used widely in oncology studies. **Overall survival (OS)** has long been established as a standard endpoint/ outcome measure used in oncology clinical trials and has been used as a primary or secondary endpoint/ outcome measure depending on the stage of cancer under investigation. The use of OS for a study looking at treatment of metastatic melanoma is not uncommon, and has been used with trials involving the current standard of care, dacarbazine. **Progression- free survival** is accepted as a reliable endpoint and is widely used as a primary endpoint/outcome measure in clinical trials

	The final analysis for PFS was performed at the time of the interim efficacy analysis for OS. PFS was defined as the time from randomization 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. PFS for patients who had no post-baseline assessment and who did not have an event were censored on the date of randomization. The primary analysis of PFS was a comparison of the two treatment groups using an unstratified log-rank test (two-sided). The hazard ratio for progression or death for vemurafenib relative to dacarbazine and the associated 95% CI were computed using a Cox regression model. Median PFS was estimated using the Kaplan-Meier method, with 95% CI calculated using the method of Brookmeyer et al (1982). The plots of Kaplan-Meier estimate of OS for each treatment group (see Figure 10) and the associated 95% CI are provided.	when investigating a treatment effect oncology studies. It is also “cleaner” endpoint that is not subject to the diluting effects of subsequent treatments given off protocol after the end of the study treatment, particularly in studies where there is likely to be a high degree of post-discontinuation cross-over of treatments

Secondary outcome(s) and measures These included assessment of the efficacy of vemurafenib using confirmed best overall response rate (BORR), duration of response, and time to response.	**Best Overall Response Rate (Confirmed)** A hierarchical approach was to be used to evaluate the statistical significance of best overall response rate (BORR) (confirmed), expressed as a percentage. If either of the co-primary endpoints of OS or PFS met the respective criteria for statistical significance, BORR (confirmed) was evaluated for statistical significance at the 0.05 level (two-sided). Best overall response (confirmed) was defined as a complete response (CR) or partial response (PR) which was confirmed per RECIST version 1.1. (For details on RECIST version 1.1. requirements, see http://www.eortc.be/Recist/documents/RECISTGuidelines.pdf). The best overall response of CR or PR was determined on the basis of confirmed response at the next tumour assessment. Evaluable patients who did not meet these criteria were considered non-responders; this included patients who never received study treatment and treated patients for whom a post-baseline tumour assessment was not performed. The BORR and the associated 95% Clopper-Pearson CI were calculated for each treatment group. The difference in BORR between treatment groups and the associated 95% Hauck-Anderson CI were calculated. BORR was compared	These outcomes and measures are commonly accepted and currently used widely in oncology studies. **Objective response and disease control** have been utilised as secondary endpoints/outcome measures extensively and considered robust supportive evidence for PFS and OS outcomes in evaluating a treatment effect in patients. Both are considered by the oncology clinical community to be important when trying to assess the impact of a treatment on a patients' tumour and the longevity of disease control. The RECIST criteria ensure a high degree of uniformity in response assessment by different reviewers.

	between treatment groups using a Chi-squared test with Schouten correction.	
	Duration of Response Duration of response was evaluated for patients who satisfied the criteria for best overall responses (confirmed). Duration of response was 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. Because the determination of duration of response was based on a non-randomized subset of patients, formal hypothesis testing was not performed on this endpoint. The log-rank test was performed for descriptive purposes only. Median duration of response was estimated using the Kaplan-Meier method, with the 95% CI calculated using the method of Brookmeyer et al (1982).	**Duration of response** reflects the durability of the treatment effect of a given therapy, before the disease progresses or death occurs which is related to the underlying cancer.
	Time to Response Time to response was evaluated for patients who satisfied the criteria for best overall response (confirmed). Time to response was defined as the time from randomization to the date of the earliest qualifying response. Time to response	**Time to response** reflects the speed of onset of the treatment effect. If responses are slow, this can delay changing treatment to a more effective one in

	was summarized using descriptive statistics (median, 25% and 75% quartiles minimum, maximum). No formal hypothesis testing was performed for time to response.	non-responders and may ultimately affect the survival of the patient.
	Other outcomes included: • To evaluate the **tolerability and safety profile** of vemurafenib using the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI CTCAE) (version 4.0) • To further characterize the **pharmacokinetic (PK) profile** of vemurafenib • To contribute to the validation of the **cobas® 4800 BRAF V600 Mutation Test** as a companion diagnostic test for the detection of BRAFV600 mutations in DNA extracted from formalin-fixed paraffin-embedded tumour (FFPET) samples	**Safety reporting** is also a well-established standard outcome measure within oncology clinical trials owing to the nature of the condition and sometimes the toxicity of the treatments to treat the disease (e.g. haematological toxicities associated with chemotherapies). In BRIM 3, safety reporting was conducted in accordance with the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) which is an internationally recognised set of guidelines for the reporting of adverse events in oncology clinical trials. Further evaluation of the **pharmacokinetic**

		profile of any new treatment is standard practice. The **cobas® 4800 BRAF V600 Mutation Test** was developed in conjunction with the development of vemurafenib. The study population in BRIM 3 provided an opportunity to further confirm the validity of the test.
Exploratory objectives	• Overall **quality of life (QoL)** of the treatment groups using the Functional Assessment of Cancer Therapy - Melanoma (FACT-M) (Version 4) questionnaire. This was administered at baseline and on Day 1 (pre-dose) of Cycles 2, 3, 4, 6, 9 and 12, and within 28 days after documented progression. • To assess the responsiveness of melanomas carrying certain non-V600E (i.e. V600K and V600D) mutations in codon 600 of the BRAF gene to vemurafenib • To evaluate biomarkers that may be relevant: - to further predict responsiveness	**Quality of life** has become increasingly important in assessing the patients' treatment experience, particularly in a disease like melanoma where treatments have traditionally been of very limited efficacy, making the trade-off between efficacy and toxicity a difficult. FACT-M is a validated and internationally recognised tool to measure quality of life in melanoma clinical trials.

	to vemurafenib - to explain primary or acquired resistance to vemurafenib - to indicate pharmacodynamic effects of vemurafenib - to monitor the disease To evaluate the molecular characteristics of squamous cell carcinomas (SCCs) that may be observed in patients treated with vemurafenib.	

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table 10: Summary of statistical analyses in BRIM 3

ClinicalTrials.gov identifier NCT01006980 Roche trial no. NO25026 (BRIM 3)	**Description**
Hypothesis objective	The following null (H0) and alternative (Ha) hypotheses were tested to compare the distribution function of OS or PFS in vemurafenib group with the distribution function in the dacarbazine group: $H0: SUR_{R0} = SUR_{dac}$ versus $Ha: SUR_{R0} \neq SUR_{dac}$ *SUR denotes the survival distribution for OS or PFS, RO refers to vemurafenib group and dac refers to dacarbazine group.* The null hypothesis will be rejected if the p-value from an unstratified log rank test is smaller than the alpha level specified for an interim analysis (IA) or final analysis. The original primary end point was the rate of overall survival. The statistical plan was revised in October 2010 on the basis of phase 1 and 2 efficacy and safety results and after consultation with global regulatory authorities. Under the revised plan, the rates of overall survival and progression-free survival were co-primary end points. The final analysis was planned after 196 deaths, and an interim analysis was planned after 50% of the projected deaths had occurred (Pocock boundary, P≤0.028 at the interim analysis and P≤0.0247 at the final analysis by the log-rank test). According to the revised plan, the final analysis of progression-free survival would be performed at the time of the interim analysis of overall survival. Secondary end points included the confirmed response rate, duration of response, and time to response. Survival was defined as the time from randomization to death from

	any cause. Progression-free survival was the time from randomization to documented disease progression or death.
Statistical analysis	A two-sided unstratified log-rank test was used to compare survival rates in the two study groups. Hazard ratios for treatment with vemurafenib, as compared with dacarbazine, were estimated with the use of unstratified Cox regression. We estimated event–time distributions using the Kaplan–Meier method. All reported P values are two-sided, and confidence intervals are at the 95% level. Descriptive statistics are used for adverse events. This report is based on data as of December 30, 2010. The statistical hypothesis of no treatment effect (null hypothesis) versus the alternate hypothesis that the treatment groups differed was tested using two-sided test statistics. No futility analysis was planned. **Analysis population** The Intent-to-Treat (ITT) population was defined as all randomized patients, whether or not study treatment was received. The ITT population was analyzed according to the treatment assigned at randomization. The statistical analysis plan (SAP) specified that all available data for patients randomized at least 15 days prior to the interim analysis cut-off date of December 30, 2010 would be included in the OS interim analysis. Therefore at the time of the interim analysis for OS, patients in the ITT population who were randomized on or before December 15, 2010 were included in the analysis of OS (subsequently referred to as patients evaluable for OS). Study enrolment completed on December 16, 2010. The population evaluable for PFS was defined in the SAP as all ITT patients randomized at least 7 weeks prior to the OS interim analysis

	data cut-off date. The 7-week interval was chosen since, per protocol, patients will have had their first post-baseline tumour assessment CT scan 6 weeks after randomization, +/- 7 days. Prior to the interim analysis of OS, the Sponsor recognized that the interval of 7 weeks did not allow sufficient time as intended for the first tumour assessment to occur, as per the protocol the first tumour assessment was to be scheduled 6 weeks from start of treatment rather than 6 weeks from randomization. Therefore, prior to the time of the interim analysis for OS and therefore also for this CSR the 7-week interval was changed to a 9-week interval to account for up to 2 weeks between randomization and the start of treatment. Therefore all patients randomized on or before October 27, 2010 were considered evaluable for the analysis of PFS. The population evaluable for best overall response rate (BORR, confirmed) was defined in the SAP as ITT patients who were randomized at least 14 weeks before the data cut-off date used for analysis. The interval of 14 weeks was chosen because it was the minimum time needed to observe an overall response that could have been confirmed, according to the protocol-specified schedule for the first two tumour assessments (every 6 weeks, +/- 7 days). Therefore, all patients randomized on or before September 22, 2010 were considered evaluable for the analysis of BORR. The Per-Protocol (PP) population was defined as treated patients, excluding patients who violated any of the following inclusion criteria: • Histologically confirmed metastatic melanoma (surgically incurable and unresectable Stage IIIC or Stage IV, AJCC) • Positive for BRAFV600 mutation by the cobas® 4800 BRAF V600 Mutation Test • No prior systemic anti-cancer therapy for this disease • ECOG performance status 0 or 1. The PP population was analysed according to the treatment received.

	Other populations that were defined include Treated population, Safety Population and Non-BRAFV600E Mutation-Positive Population **Timing of the analysis** One interim analysis for the co-primary endpoint of OS was planned. The final analysis of the co-primary endpoint of PFS was planned to occur at the time of the interim analysis of OS. Review of the interim analysis results was performed by an external Data Safety Monitoring Board (DSMB).
Sample size, power calculation	The trial was designed for 680 patients to be randomly assigned (1:1) to receive either vemurafenib or dacarbazine. The trial had a power of 80% to detect a hazard ratio of 0.65 for overall survival with an alpha level of 0.045 (an increase in median survival from 8 months for dacarbazine to 12.3 months for vemurafenib) and a power of 90% to detect a hazard ratio of 0.55 for progression- free survival with an alpha level of 0.005 (an increase in median survival from 2.5 months for dacarbazine to 4.5 months for vemurafenib). **Overall Survival** It was estimated based upon the assumptions below that a total of 196 deaths (100% information) provided 80% power to detect a hazard ratio of 0.65 for death for vemurafenib treatment relative to dacarbazine treatment: • 0.045 significance level (two-sided) • Log-rank test (two-sided) • Median survival of 8 months in the dacarbazine arm and 12.3 months in the vemurafenib arm

	• Accrual of 41 patients per month • One interim analysis for OS at 50% information **Progression-Free Survival** It was estimated based on the assumptions below that 187 PFS events would have occurred by the time of the interim analysis of OS. A total of 187 PFS events (disease progression or death) provided 90% power to detect a hazard ratio of 0.55 for vemurafenib treatment relative to dacarbazine treatment, under the following assumptions: • 0.005 significance level (two-sided) • Log-rank test (two-sided) • Median PFS of 2.5 months in the dacarbazine arm and 4.5 months in the vemurafenib (The type 1 error (alpha) for this study was 0.05 (two-sided). There were two co-primary efficacy endpoints for this study: overall survival (OS) and progression-free survival (PFS). To maintain the alpha level of 0.05 (two-sided) while accounting for two co-primary endpoints, statistical significance for the comparison of OS was based on an alpha level of 0.045 (two-sided), and statistical significance for the comparison of PFS was based on an alpha level of 0.005 (two-sided))
Data management & patient withdrawals	The contract research organization (CRO), Quintiles (UK office), provided site management, data management, monitoring, and project management support. Data management was performed by the US office of Quintiles. Accurate and reliable data collection was assured by verification and cross-check of the electronic case report forms (eCRF) against the investigator's records by the study monitor (source document verification) and the maintenance of a study drug dispensing log by the investigator. Data from paper source documents were entered by the site onto the eCRF.

	A comprehensive validation check program was used to verify the data and discrepancy reports were generated accordingly for resolution by the investigator. Efficacy analyses were performed in the intention-to-treat population. In order to ensure adequate follow-up for each efficacy end point, patients could be evaluated for the analysis of overall survival, progression-free survival, and confirmed response if they had undergone randomization at least 2, 9, and 14 weeks, respectively, before the cut-off date. The safety analysis was performed in all patients who received a study drug and who had undergone at least one assessment during the study.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Analyses, including forest plots (see Figure 9, Figure 11), are provided for OS and PFS for patient subgroups including:

- Age (years) at randomization (< 65, ≥ 65) and (< 40, 41−54, 55−64, 65−74, ≥ 75)
- Race (Non-White, White)
- Sex (female, male)
- Region (North America, Western Europe, Australia/New Zealand, other)
- ECOG performance status at randomization (0, 1)
- Metastatic classification at randomization (unresectable stage IIIC, M1a, M1b, M1c)
- Lactate Dehydrogenase (LDH) at randomization (normal, elevated)

- Brain metastases at baseline (no, yes)

Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Patient Disposition in BRIM 3

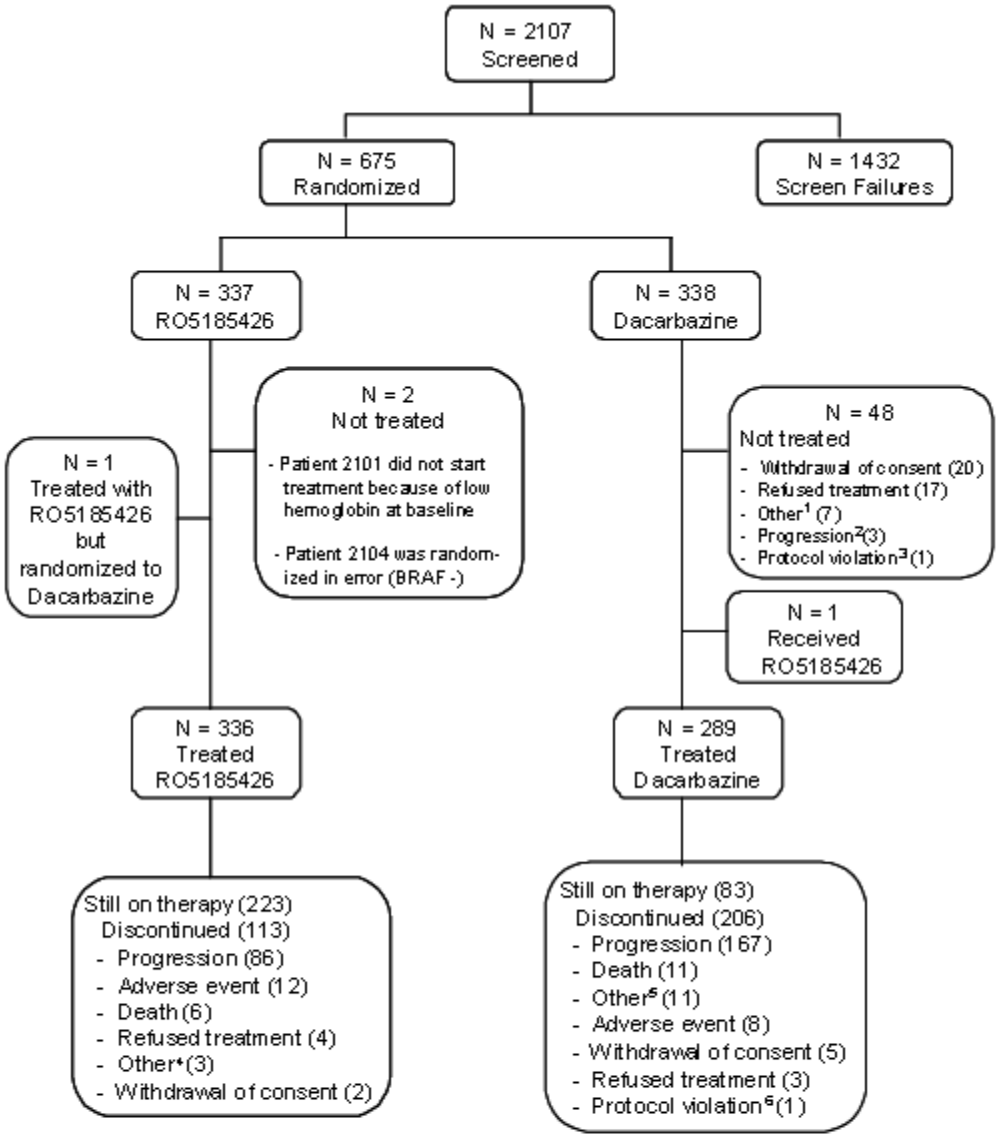
A total of 2107 patients underwent screening at 104 centres in 12 countries worldwide between January 2010 and December 2010. The most common reason for screening failure was a negative test for the BRAF V600 mutation.

A total of 675 patients were randomly assigned in a 1:1 ratio to receive either vemurafenib (at a dose of 960 mg twice daily orally) or dacarbazine (at a dose of 1000 mg per square metre of body-surface area by intravenous infusion every 3 weeks). These patients included 20 with non-V600E mutations (19 with V600K and 1 with V600D), as identified on Sanger and 454 sequencing.

Study patients were stratified according to American Joint Committee on Cancer stage (IIIC, M1a, M1b, or M1c), ECOG performance status (0 or 1), geographic region (North America, Western Europe, Australia or New Zealand, or other region), and serum lactate dehydrogenase level (normal or elevated).

The disposition of patients recruited into BRIM 3 is shown below in Figure 6.

Figure 6: BRIM 3 Patient Disposition - Data as of December 30, 2010



Dacarbazine - Not treated

1- *Other:* Pulmonary embolism prior to treatment (1 pt); Not eligible per exclusion criteria (1 pt); clinical deterioration (1 pt); brain metastases (2 pts); 2 patients pending resolution on treatment status

2- *Progression:* pending resolution on treatment status (2 pts) and clinical deterioration listed as disease progression prior to treatment (1 pt)

3- *Protocol Violation:* no measurable disease (1 pt)

RO5185426 - Treated

4- *Other:* Disease Progression (3 pts)

Dacarbazine - Treated

5- *Other:* Patient/Investigator/medical decisions (6 pts); progressive disease/clinical deterioration (4 pts); adverse event (1 pt)

6- *Protocol violation:* BRAF V600E mutation negative randomized in error (received 1 infusion of dacarbazine) (1 pt)

5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Table 11: Quality assessment results for BRIM 3

Quality Assessment question	**Response for BRIM 3 RCT**
Was the method used to	Yes. After archival tumour samples for each patient

generate random allocations adequate?	tested positive for the BRAFV600 mutation using the cobas® 4800 BRAF V600 Mutation Test and all other eligibility criteria were met, patients were randomly assigned in a 1:1 ratio to open-label treatment with either vemurafenib or dacarbazine. The randomization was designed to minimize imbalances between treatment groups within the 4 stratification factors (stratified according to American Joint Committee on Cancer stage (IIIC, M1a, M1b, or M1c), ECOG performance status (0 or 1), geographic region (North America, Western Europe, Australia or New Zealand, or other region), and serum lactate dehydrogenase level (normal or elevated)). Patients randomized into the study were not replaced. A centre could be replaced because of excessively slow recruitment or poor protocol adherence.
Was allocation adequately concealed?	While the treatments within the study were not blinded, adequate concealment of the randomisation occurred by using an interactive voice recognition system (IVRS).
What randomisation technique was used?	Randomization was performed by Almac Clinical Technologies, Yardley, PA, using aninteractive voice recognition system (IVRS).
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No – see above for details of blinding. Given the poor prognosis and high levels of morbidity in this patient group it would have ethically problematic to subject patients in the study to tests and procedures not relevant to their allocated therapy as would have been required in a blinded study. In particular it would have been hard to justify giving patients, already taking an oral therapy (vemurafenib), 3-weekly injections of placebo. Furthermore, knowledge of treatment allocation is unlikely to influence OS, one of

	the co-primary end-points
Was a justification for sample size provided?	Yes, based on the statistical requirement to demonstrate a predetermined treatment effect with a specified degree of statistical certainty. The sample size calculation was based on explicit assumptions about the clinical behaviour of the patient group in question and the impact of treatment.
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes – see Table 8
Was follow-up adequate?	The initial data set from December 2010 was produced at the time of the pre-planned interim analysis of overall survival. This together with the final analysis of progression-free survival formed the basis for the US regulatory submission. See 5.3.1 for further information. Between January 4, 2010 and December 16, 2010, a total of 675 patients were randomized to this study: 337 patients to vemurafenib and 338 patients to dacarbazine. The DSMB for Study NO25026 recommended release of the results of this study due to compelling efficacy based on review of results presented January 14, 2011 at the time of the planned interim analysis of OS. The final analysis of PFS was performed as planned at the time of the interim analysis of OS. As already stated, the US regulatory submission was

	based upon the initial interim analysis of the data set from December 2010. This involved limited follow-up of the two cohorts - Median follow-up for the interim analysis was 3.8 months for patients in the vemurafenib group and 2.3 months for those in the dacarbazine group. At the time of the interim analysis, there were an inadequate number of patients in follow-up beyond 7 months in either study group to provide reliable Kaplan–Meier estimates of the survival curves. At 6 months, overall survival was 84% (95% CI, 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine group. Further follow-up was required. A further cut of data was performed in March 2011. Analysis of this data was performed and the results were presented at ESMO 2011 by Dr. G. McArthur. This data showed that the median OS had not yet been reached for patients receiving vemurafenib. The median OS for those patients receiving dacarbazine was 7.9 months. Follow-up was on-going. The most recent cut of data was performed in October 2011, involving the OS only. This was done to assist the EMA with the regulatory submission for vemurafenib. The results are included in this HTA submission – the median OS for patients receiving vemurafenib was 13.2 months. The median OS for those patients receiving dacarbazine was 7.9 months. With considerable numbers of patients being followed up, the data set is still immature and subsequent analyses of further data-cuts are expected. However, the superiority of vemurafenib over the current standard of care, dacarbazine, has been

	demonstrated. Given the magnitude of the superiority it is implausible that it will not endure as the data matures.
Was the design parallel group or cross-over?	The study was designed as a parallel group. However protocol amendments allowed cross-over following the interim OS analysis. A total of 118 patients had died at the time of the interim analysis. The data and safety monitoring board determined that both the overall survival and progression-free survival end points had met the pre-specified criteria for statistical significance in favour of vemurafenib. The board recommended that patients in the dacarbazine group be allowed to cross over to receive vemurafenib, and the protocol was amended accordingly on January 14, 2011. This could reduce the impact of the trial intervention on the secondary end-point of OS going forward but it would have been unethical to continue patients on the dacarbazine therapy with the knowledge that this was less efficacious treatment compared to vemurafenib with regards to response rate.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.
Was the RCT conducted	No. BRIM 3 was an international multi-centre study.

in the UK?	There were 14 sites within the UK, recruiting 74 out of 672 patients.
How do RCT participants compare with the clinical population of patients within the UK?	There is no reason to suppose that patients recruited into this study are not representative of the population of previously untreated patients with unresectable stage IIIC or stage IV melanoma receiving chemotherapy in routine clinical practice in the UK. UK oncologists are accustomed to seeing patients with previously untreated unresectable stage IIIC or stage IV melanoma. For those with reasonable performance status (PS 0 or 1) like those entered into BRIM 3, chemotherapy would generally be offered, with dacarbazine being the standard of care in the absence of a suitable clinical trial
Were the study groups comparable?	Table 8: Baseline characteristics of shows that patients in the control and experimental arms of BRIM 3 were well matched in terms of demographic, disease and treatment characteristics.
Were the statistical analyses undertaken appropriate?	Yes. The manipulation of data from the study was undertaken according to a clear plan (the DRAM) finalised with expert statistician input prior to the availability of study data
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. This was the primary analysis. This was appropriate for this RCT. Patients who were lost to follow-up or who had crossed over from the dacarbazine to the vemurafenib treatment arm were censored. For patients who were alive at the time of analysis data cut-off, OS was censored at the last date the

	patient was known to be alive prior to the clinical cut-off date (30th December 2010). The last date the patient was known to be alive was derived as the latest date of contact or study assessment. Survival time for patients with no post-baseline survival information was censored on the date of randomization. With regards to progression-free survival, patients who had neither progressed nor died were censored on the date of last evaluable tumour assessment prior to the clinical cut-off date. PFS for patients who had no post-baseline assessment and who did not have an event were censored on the date of randomization. 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.
Are there any other confounding factors that may attenuate the interpretation of the results of the RCTs?	Patients were allowed to cross-over post-progression. This would be likely to attenuate any impact of study treatment on the co-primary end-point of OS but not the primary PFS endpoint (see Table 14). However, the data shows the superiority of vemurafenib over dacarbazine at the first data-cut (December 2010) which was first published in the NEJM (Chapman et al, 2011). At that time, 50 (15%) patients had crossed over from the dacarbazine to the vemurafenib arm. At further follow-up (October data-cut), overall survival was greater with vemurafenib (13.2 months) than dacarbazine (9.6 months) – censored results at the time of cross-over.

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table 12: Quality assessment results for BRIM 3

ClinicalTrials.gov Identifier: NCT01006980. **Roche trial no. NO25026**	**BRIM 3**
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Some secondary end-points have not yet been presented e.g. pharmacokinetics, Quality of Life
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

5.5 Results of the relevant RCTs

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

All results are provided under heading 5.5.3.

5.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

All results are provided under heading 5.5.3.

5.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Table 13: Reliability and Validity of Primary and secondary outcomes of the BRIM 3

ClinicalTrials.gov Identifier: NCT01006980. Roche trial no. NO25026 (BRIM 3)		**Vemurafenib**	**Dacarbazine**	**Reliability/validity/ current use in clinical practice**
Primary outcomes and measures (vemurafenib n =337, dacarbazine n = 338)	Medial overall survival (months)*	13.2	9.6	See **Table 9**
		See Table 14 for Hazard Ratios and OS from previous data set cut-offs		
	Overall survival at 6 months (%) **:	84 (95% CI, 78 to 89)	64 (95% CI, 56 to 73)	
	Median progression-free Survival (n=549)*** (months)	5.32 (4.86 to 6.57)	1.61 (1.58 to 1.74)	
		Hazard Ratio (95% CI) 0.26 (0.20, 0.33)		
Secondary outcomes and measures (vemurafenib n =219, dacarbazine n = 220)	Confirmed Response Rate no. (%)***	48.4% 95% CI, 42 to 55 (106/219 evaluable patients) Complete response: 104 Partial response: 2	12 (5.4); 95% CI, 3 to 9	See **Table 9**
	Duration of response (months)***	5.49 (1.22 to 7.62)	Not reached	
	Median time to response (months)***	1.45	2.7	

** 3 October 2011 data set cut-off: Zelboraf (vemurafenib) Summary of Product Characteristics RXUKZELB00029 (December 2011)*

*** 31 March 2011 data set cut-off: McArthur GA et al. Vemurafenib improves overall survival compared to dacarbazine in advanced BRAFV600E-mutated melanoma: Updated survival results from a Phase III randomised, open-label, multicentre trial (Abstract #28LBA). ECCO/ESMO 2011*

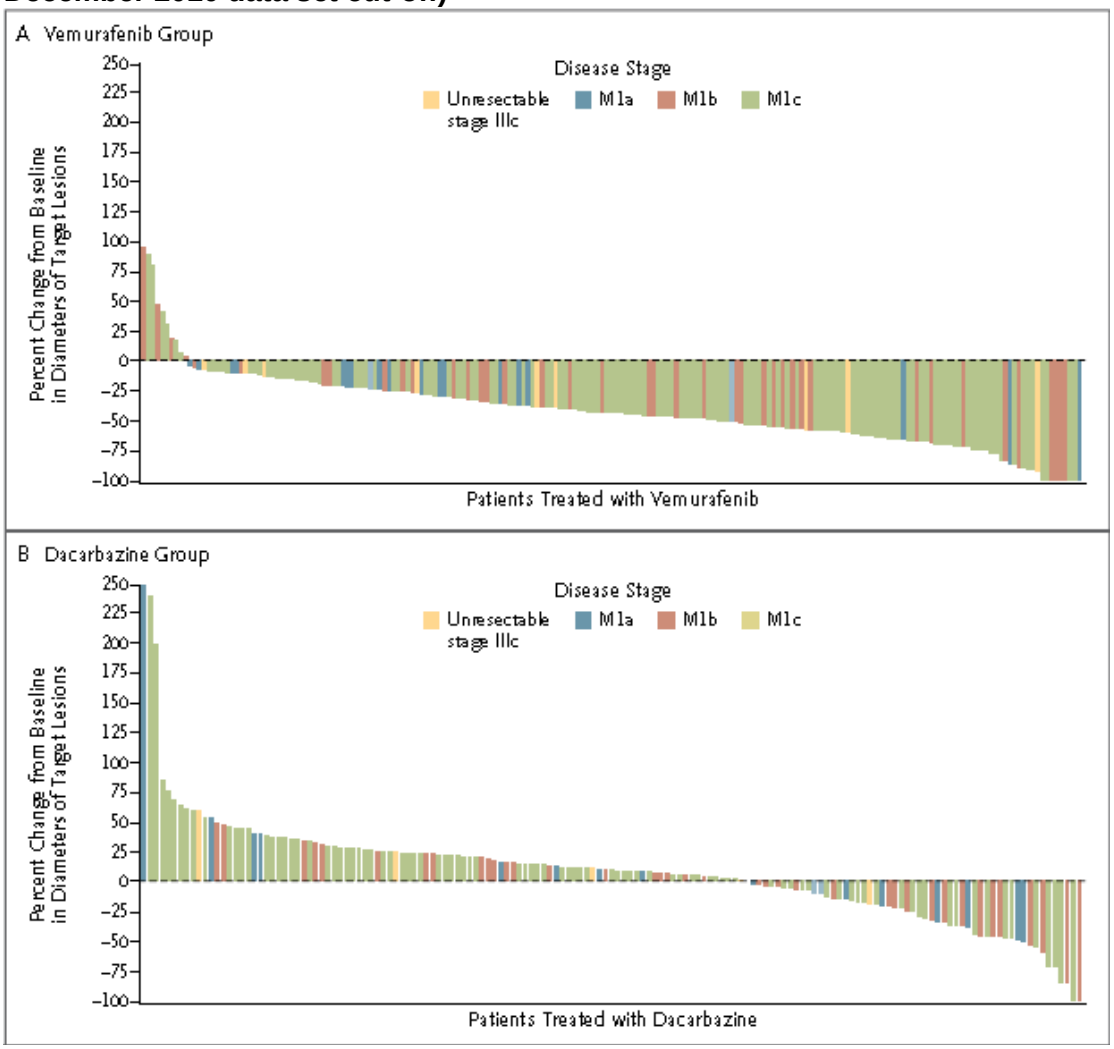
**** December 2010 data set cut-off: Clinical Study Report – NO25026 –BRIM 3. Research*

Initial data set: 30th December 2010 (including Interim analysis for OS)

A total of 672 patients were evaluated for overall survival (see Figure 8). The hazard ratio for death in the vemurafenib group was 0.37 (95% confidence interval [CI], 0.26 to 0.55; P<0.001). The survival benefit in the vemurafenib group was observed in each pre-specified subgroup, according to age, sex, ECOG performance status, tumour stage, lactate dehydrogenase level, and geographic region (see Figure 9). At the time of the interim analysis, there were an inadequate number of patients in follow-up beyond 7 months in either study group to provide reliable Kaplan–Meier estimates of OS. At 6 months, overall survival was 84% (95% CI, 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine group.

Progression-free survival was evaluated in 549 patients (see Figure 10). The hazard ratio for tumour progression in the vemurafenib group was 0.26 (95% CI, 0.20 to 0.33; P<0.001). The estimated median progression-free survival was 5.3 months in the vemurafenib group and 1.6 months in the dacarbazine group. Superior progression-free survival with vemurafenib over dacarbazine was observed in all subgroups that were analysed (see Figure 11).

Figure 7: Waterfall Plot showing best tumour response for each patient (30 December 2010 data set cut-off)



A total of 439 patients (65%) could be evaluated for tumour response on the basis of having undergone randomization less than 14 weeks before the clinical cut-off date of December 30, 2010 (see Figure 7). In the vemurafenib group, most patients had a detectable decrease in tumour size, and 106 of 219 patients (48%; 95% CI, 42 to 55) had a confirmed objective response (including 2 patients with a complete response and 104 with a partial response), with a median time to response of 1.45 months.

In the dacarbazine group, a minority of patients had a detectable decrease in tumour size, and only 12 of 220 patients (5%; 95% CI, 3 to 9) met the criteria

for a confirmed response (all partial responses), with a median time to response of 2.7 months. The difference in confirmed response rates between the two study groups (48% vs. 5%) was highly significant (P<0.001 by the chi-square test) – the results are summarised in **Error! Reference source not ound.**.

Figure 8: Interim analysis of BRIM 3 overall survival

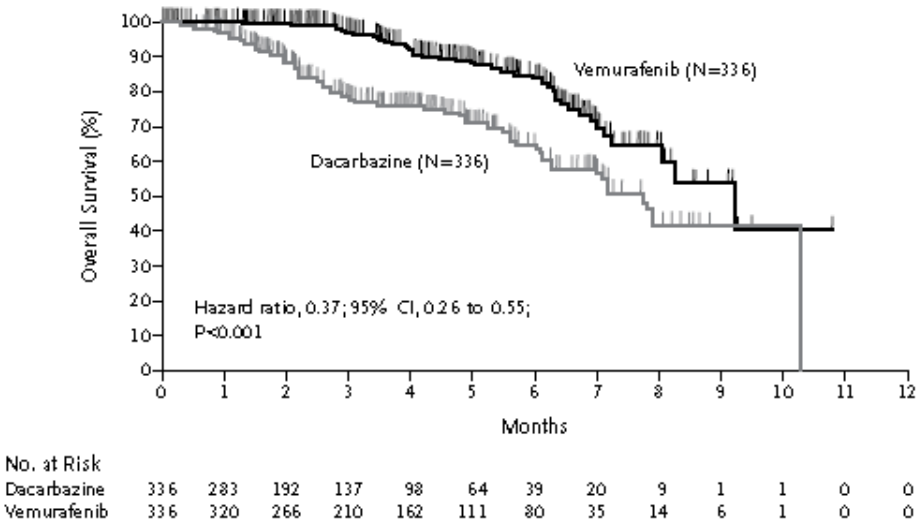


Figure 9: Sub-group analyses for the interim analysis of overall survival for BRIM 3

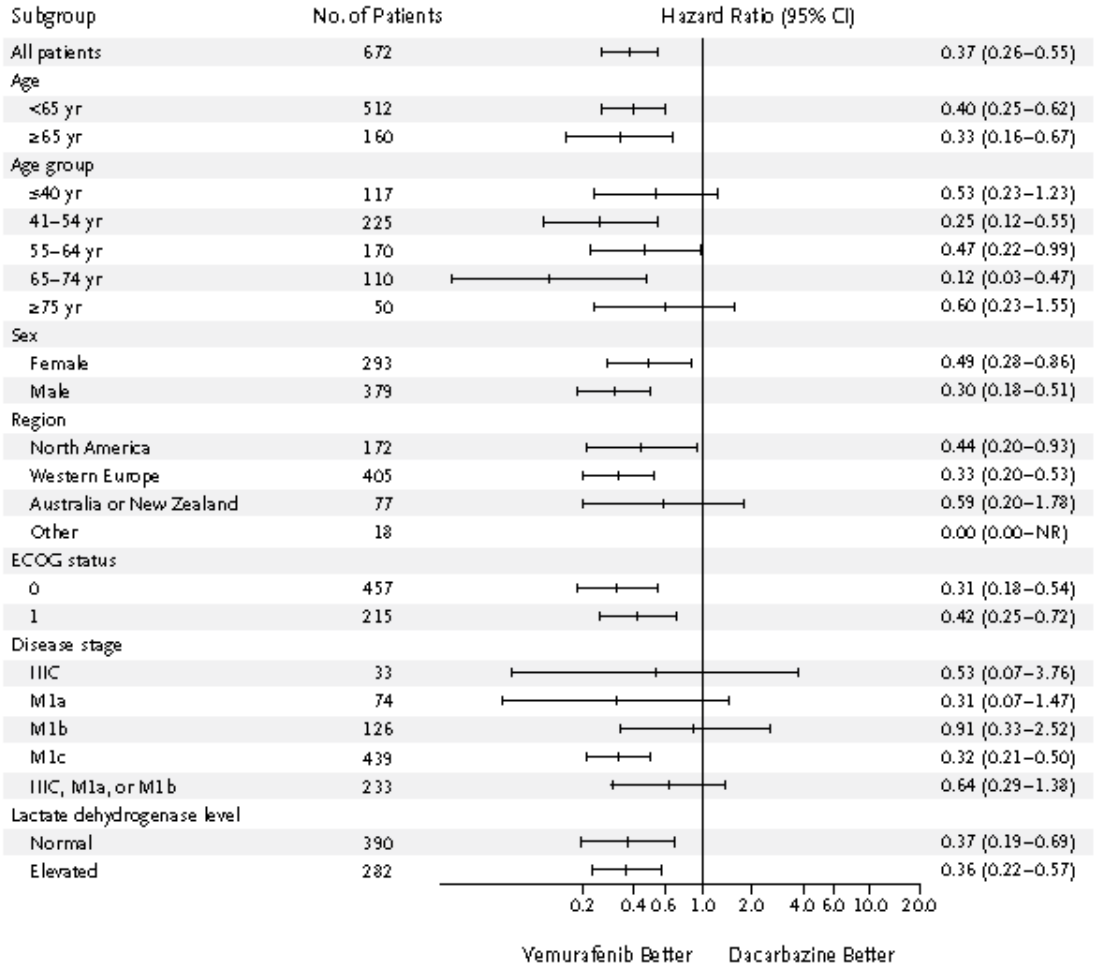


Figure 10: Progression-free survival for BRIM 3 (30 Dec 2010, final pre-planned analysis at interim analysis)

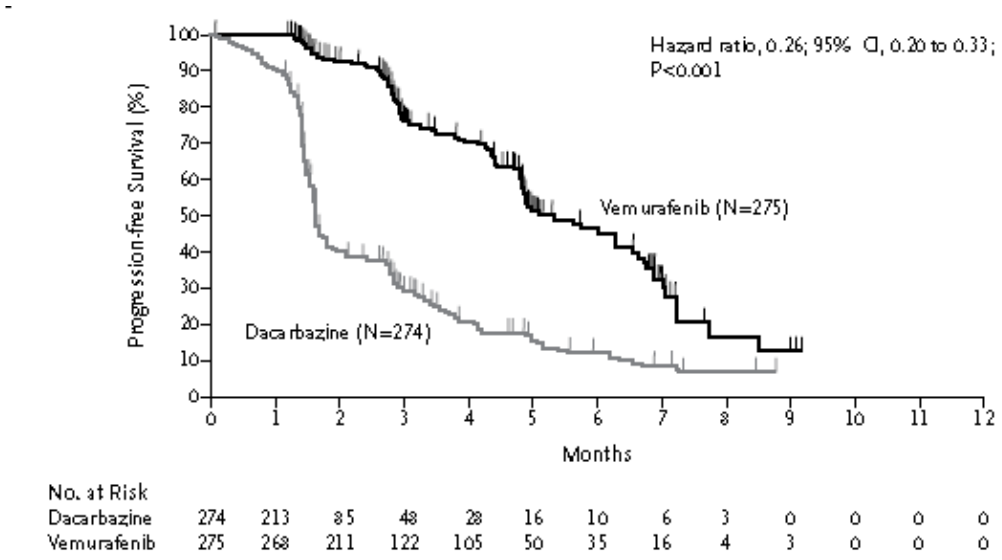
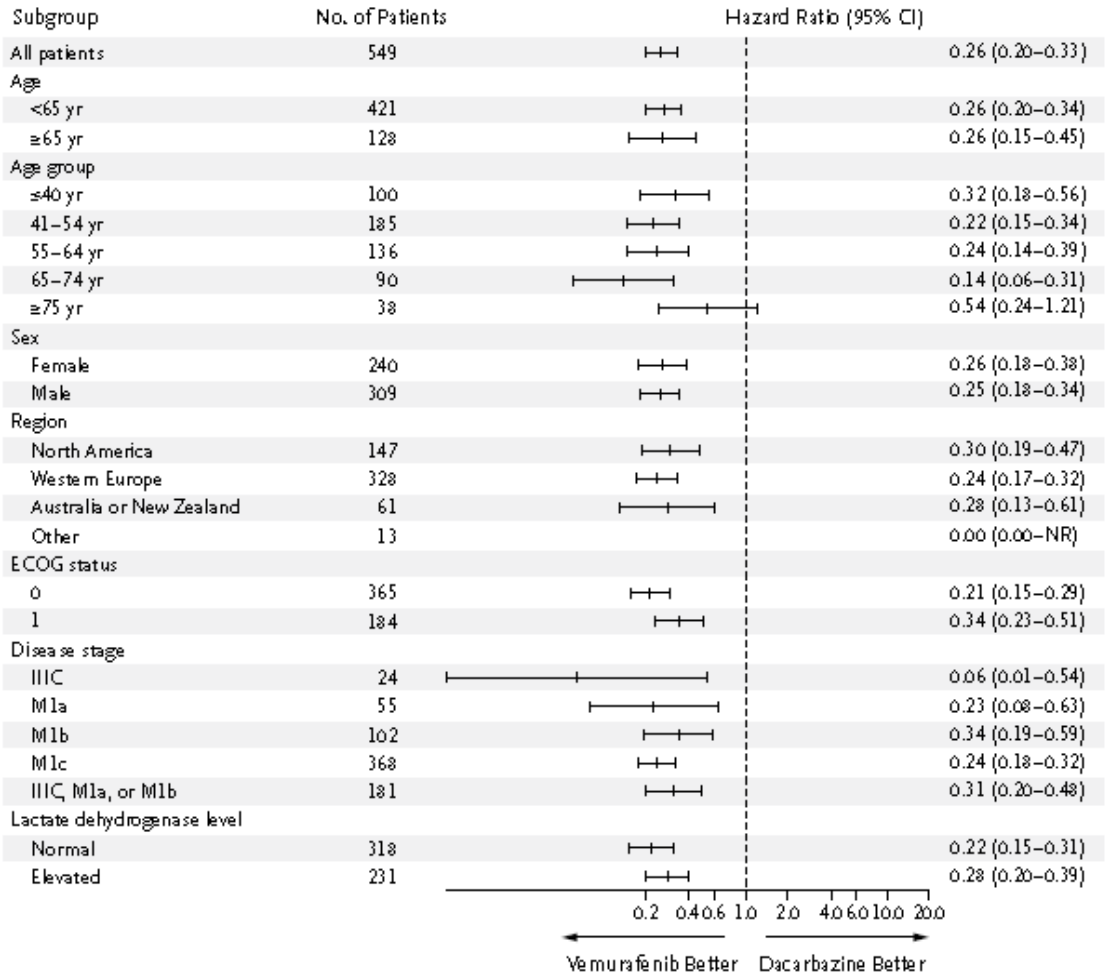


Figure 11: Sub-group analyses of progression-free survival for BRIM 3



5.5.3.1 Updated Analysis for BRIM 3

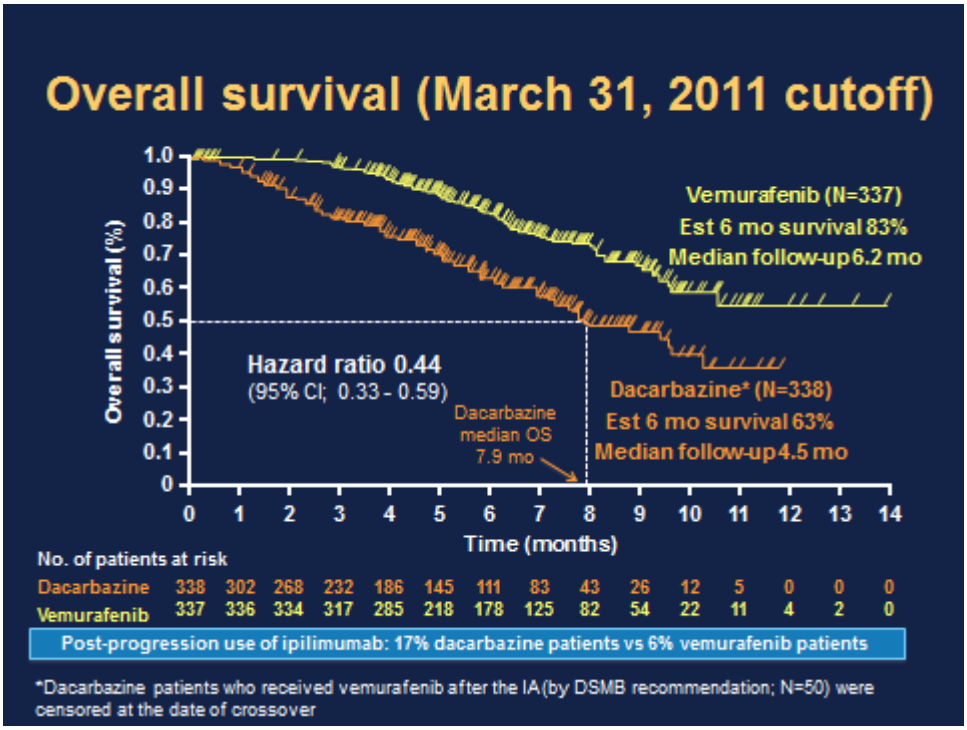
The survival data has evolved as the data has matured. To date, two further analyses of the data have been produced, in March and October 2011. From these, a pattern of overall survival can be seen.

A. Data set: 31st March 2011

Following the interim analysis in December 2010, a further evaluation was made and presented at The European Multidisciplinary Cancer Congress, Stockholm 23 – 27 September 2011 (see Figure 12). At this stage in the follow-up of the two treatment arms, median overall survival had not yet been reached within the vemurafenib treatment group. Median overall survival had

been reached for the dacarbazine arm, with median OS of 7.9 months (Hazard ratio 0.44, 95% CI: 0.33-0.59).

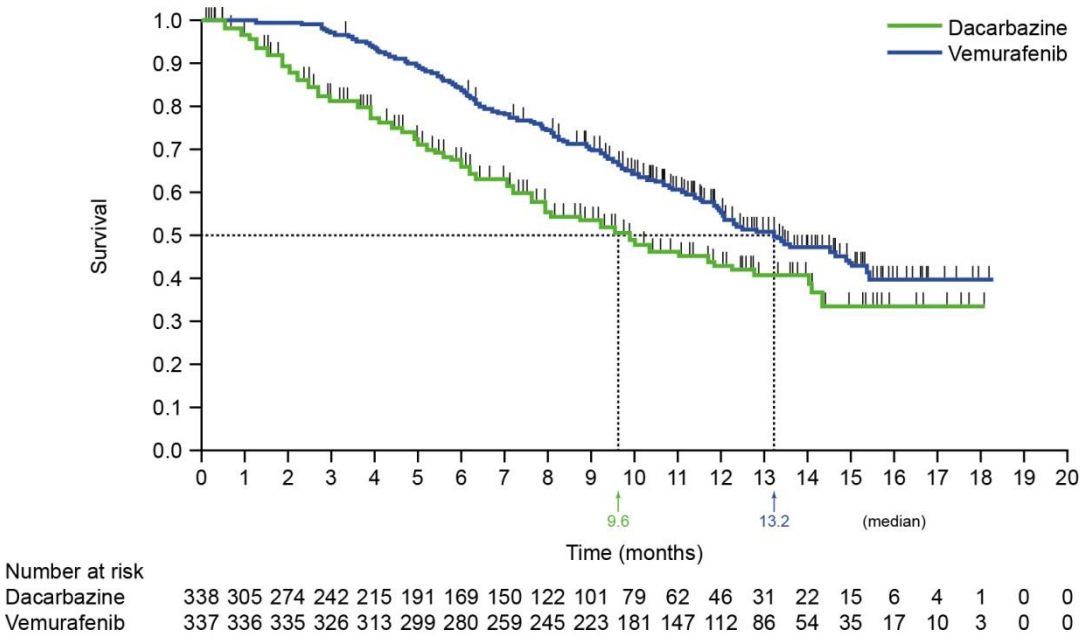
Figure 12: Updated results: Kaplan-Meier estimates of overall survival for BRIM 3 (data set from March 31st 2011 analysis)



B. Data set: 3rd October 2011

Further analysis of the BRIM 3 data showed the median overall survival for the vemurafenib treatment group had been reached, with a median OS of 13.2 months (see Figure 13). At this stage, the median OS for the dacarbazine arm was 9.6 months.

Figure 13: Updated results: Kaplan-Meier estimates of overall survival for BRIM 3* (data set from October 3 2011 cut-off)



See Table 14 for Hazard Ratios.

5.5.3.2 Cross-over of patients in BRIM 3

It was decided that it would be unethical for patients in the dacarbazine treatment to continue receiving this treatment without being offered the option to cross over to the vemurafenib arm. By the time of the most recent data set (3 October 2011), almost a quarter of all dacarbazine patients had crossed over to the vemurafenib arm. Table 14 summaries the overall survival at each data cut, and the degree of crossover.

Table 14 Overall survival by BRIM 3 cut-off dates (n=338 dacarbazine, n=337 vemurafenib)

Cut-off dates	Treatment	Number of deaths (%)	Hazard Ratio (95% CI)	Number of cross-over patients (%)
December 30, 2010	dacarbazine	75 (22)	0.37 (0.26, 0.55)	0 (not applicable)
	vemurafenib	43 (13)		
March 31, 2011	dacarbazine	122 (36)	0.44 (0.33, 0.59)*	50 (15%)
	vemurafenib	78 (23)		
October 3, 2011	dacarbazine	175 (52)	0.62 (0.49, 0.77) *	81 (24%)
	vemurafenib	159 (47)		

* Censored results at time of cross-over

Non-censored results at time of cross-over: March 31: HR (95% CI) = 0.47 (0.35, 0.62); October 3: HR (95% CI) = 0.67 (0.54, 0.84)

5.5.3.3 Non-BRAF V600E mutations in BRIM 3

A total of 19 patients out of 220 whose tumours were analysed by retrospective sequencing were reported to have BRAF V600K mutation-positive melanoma in NO25026. Although limited by the low number of patients, efficacy analyses among these patients with V600K-positive tumours suggested a treatment benefit of vemurafenib in terms of OS (HR 0.27; 95% CI: 0.05, 1.51), PFS (HR 0.09, 95% CI, 0.02, 0.45) and confirmed best overall response (4 responders among the 10 patients). No further data are available in patients with melanoma harbouring BRAF V600 mutations others than V600E and V600K.

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.

- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Not applicable. Only one RCT investigating the efficacy of vemurafenib is available.

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

As above.

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

As above.

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

BRIM3 featured a comparison of vemurafenib to dacarbazine in previously untreated BRAF V600 mutation positive patients. An indirect comparison of the two agents is therefore unwarranted.

As discussed in section 4 a case for NICE approval of vemurafenib in a previously treated setting has not been presented.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Not applicable.

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Not applicable.

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

Not applicable.

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Not applicable.

5.7.6 Please present the results of the analysis.

Not applicable.

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Not applicable.

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable.

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable.

5.8 Non-RCT evidence

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the

presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

5.8.1.1 Identification of studies

Dialogue ProQuest (Embase, Embase Alert, Medline (including in process)) and the conference abstract databases displayed below were searched for non-randomised evidence on the efficacy of vemurafenib.

- ASCO at www.asco.org
- ECCO at http://annonc.oxfordjournals.org
- European Multidisciplinary Cancer Congress 2011 at http://stockholm2011.ecco-org.eu
- 8th and 9th International Symposium on Targeted Anticancer Therapies at http://annonc.oxfordjournals.org
- 7th International Melanoma Congress Sydney 2010 at www.melanoma2010.org

The search strategies for the conference sites did not specify RCT in the terms used. ASCO was searched with a free-text search for 'vemurafenib' and 'melanoma', 'RG7204' and 'melanoma', 'PLX4032' and 'melanoma', and 'Zelboraf' and 'melanoma'. The 8th and 9th International Symposium on Targeted Anticancer Therapies, and the 7th International Melanoma Congress websites were searched with 'BRAF', vemurafenib, RG7204, and PLX4032 as search terms. The ESMO abstracts were searched on the Annals of Oncology site, with the terms BRAF, vemurafenib, RG7204, and PLX4032.

The European Multidisciplinary Cancer Congress 2011 was searched online at http://stockholm2011.ecco-org.eu for the term vemurafenib.

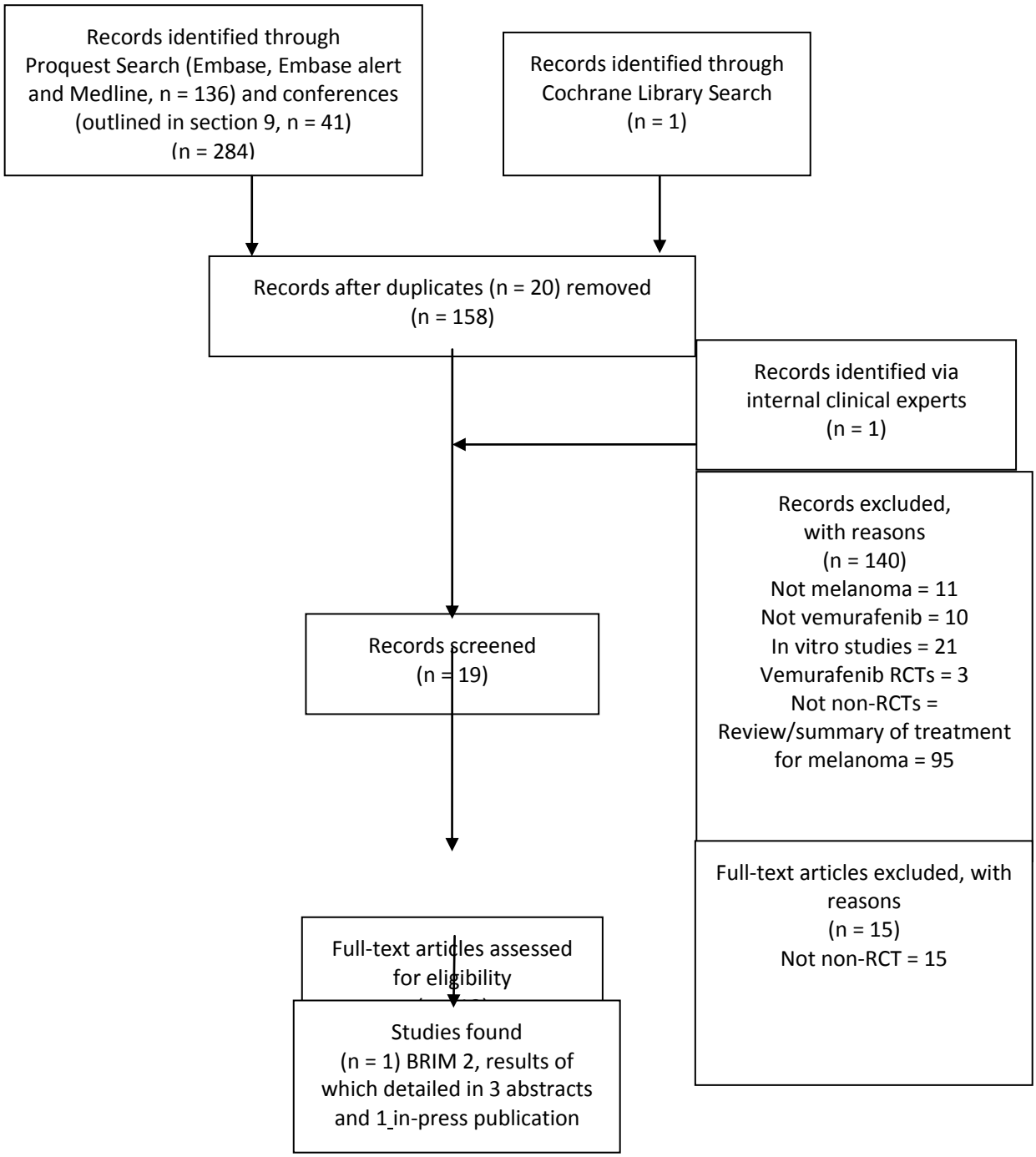
Search results were assessed according to the following predefined inclusion/exclusion criteria:

Table 15: Eligibility criteria used in search strategy

	Inclusion Criteria	Exclusion Criteria
Population	Previously untreated unresectable or metastatic melanoma patients with BRAF V600 mutation-positive	Patients with non-metastatic or resectable melanoma, with BRAF mutation negative status
Interventions	Vemurafenib monotherapy	Non-vemurafenib therapy
Comparators	Accepted drug therapy standard of care : Dacarbazine therapy	Investigational Agents, non-standard of care
Outcomes	Progression Free Survival, Overall Survival, Adverse Events	-
Study Design	Observational data, registry analyses, single arm studies, meta-analyses	Randomised controlled trials, phase 1/dose ranging studies

The search flow is detailed in the PRISMA diagram below. Following consultation with internal experts on the vemurafenib clinical trial program it was noted that a publication of the BRIM2 study has been accepted for publication in the NEJM (due to be published in Q1 2012). Whilst not yet published this data was added to the search in order to ensure all relevant data was captured.

Figure 14: PRISMA Flow-chart of vemurafenib non-RCT search



In total the search identified one non-randomised study investigating vemurafenib; the BRIM2 study.

There are several sources of information for this study

1. Ribas A et al. BRIM2: An Open-label, Multi-centre Phase II Study of Vemurafenib (PLX4032, RG7204) in Previously Treated Patients with BRAFV600E Mutation-positive Metastatic Melanoma. ASCO 2011 (Abstract #8509)

2. Bloom KJ et al. Molecular testing for BRAF V600 mutations in the BRIM-2 trial of the BRAF inhibitor vemurafenib in metastatic melanoma. ASCO 2011: J Clin Oncol 2011; 29: (15 supp) abstract 10523

3. Sosman J et al. An open-label, multi-centre phase II study of continuous oral dosing of RG7204 (PLX4032) in previously treated patients with BRAF V600E mutation positive metastatic melanoma. 7th International Melanoma Congress 2010 Sydney

4. The full study is to be published in early 2012 - Sosman JA et al. Long-term follow-up of BRAFV600mutated metastatic melanoma patients treated with vemurafenib reveals prolonged survival.(NEJM, in-press)

The results of the phase 1 'BRIM1' study (ClinicalTrials.gov Identifier: NCT00405587) of vemurafenib are not presented below as this study was only a dose-ranging study of relatively small sample size.

Table 16: Relevant non-RCTs: ClinicalTrials.gov Identifier NCT00949702; Roche trial no. NP22657 (BRIM-2)

Interv-ention	Population	Objectives	Primary study ref.	Justification for inclusion
Vemur-afenib	Previously treated BRAF mutation-positive metastatic melanoma patients	To confirm the ORR and anti-tumour activity of vemuraf-enib in previously treated patients with BRAF V600-mutated melanoma	1. Ribas A et al. BRIM-2: An open-label, multicentre phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma. J Clin Oncol 29: 2011 (suppl; abstr 8509); 2. Sosman JA et al. Long-term follow-up of BRAFV600mutated metastatic melanoma patients treated with vemurafenib reveals prolonged survival. NEJM 2012; 3. Clinical Study Report – NP22657: An Open-Label, Multi-Centre, Phase II Study of Continuous Oral Dosing of vemurafenib in Previously Treated Patients With Metastatic Melanoma. Report No. 1038633. April 2011	Provides data on tolerability, safety and efficacy in previously treated metastatic melanoma patients.

5.8.1.3 Summary of methodology of relevant studies

Table 17 Comparative summary of methodology of the BRIM2

Trial no. **(acronym)**	**ClinicalTrials.gov Identifier: NCT00949702** **Roche trial no. NP22657 (BRIM2)**
Location	USA, Australia
Design	single arm, multicentre, phase 2 clinical trial
Duration of study	Between October 2009 and March 2010, 344 patients were screened for study entry. The efficacy data cut-off was July 1, 2011, with median follow-up of 13 months (range 0.6 to 20.1 months). The safety data cut-off was January 31, 2011, with median follow-up of 10 months (range 0.6 to 14.7 months).
Method of randomisation	Non-randomised
Method of blinding (care provider, patient and outcome assessor)	Open label study
Intervention(s) (n =) and comparator(s) (n =)	vemurafenib 960 mg orally twice daily (n=132) No comparator
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint was ORR assessed by independent central radiologic review. The ORR was defined as the number of patients with a complete response (CR) or partial response (PR) divided by the total number of treated patients. To be assigned a status of PR or CR, the change in tumour measurements had to be confirmed by ≥1 repeat tumour assessment performed sequentially ≥28 days after the criterion for response was first met. ORR was calculated with corresponding exact two-sided 95% CI using the Clopper-Pearson method.
Secondary outcomes (including scoring methods and timings of assessments)	Overall survival (OS)
Duration of follow-up	The efficacy data cut-off was July 1, 2011, with median follow-up of 13 months* (range 0.6 to 20.1 months). The safety data cut-off was January 31, 2011, with median follow-up of 10 months* (range 0.6 to 14.7 months). *At the time of publication of the data in the NEJM, 2012

Participants

Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table 18: Eligibility criteria in the BRIM2

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
ClinicalTrials.gov Identifier: NCT00949702 **Roche trial no. NP22657 (BRIM2)**	Patients had to meet all of the following criteria to be included in the study: 1. Male or female ≥ 18 years of age 2. Histologically confirmed metastatic melanoma (Stage IV, American Joint Committee on Cancer) 3. Must have completed and failed at least one prior standard of care regimen (e.g., DTIC, temozolomide, etc.) 4. Must have a *BRAF*$_{V600}$ mutation-positive melanoma (using the Roche cobas® 4800 BRAF V600 Mutation Assay) prior to administration of vemurafenib 5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 6. Measurable disease (by RECIST Version 1.1) prior to administration of vemurafenib 7. Must have recovered from effects of any major surgery at least 14 days before the first dose of study treatment 8. Adequate hematologic, renal, and liver function as defined by the following laboratory values performed within 28 days prior to initiation of dosing: • Absolute neutrophil count ≥ 1.5 x 10^9/L • Platelet count ≥ 100 x 10^9/L • Haemoglobin ≥ 9 g/dL • Serum creatinine ≤ 1.5 times the upper limit of normal (ULN) or creatinine clearance > 40 ml/h by the	Patients meeting any of the following criteria were excluded from the study: 1. Any active CNS lesion. (Each patient had a head CT/MRI test to evaluate for CNS metastasis within 28 days prior to enrolment. Patients with radiographically stable, asymptomatic lesions previously irradiated by stereotactic therapy, or surgically removed lesions, were eligible provided they were ≥ 3 months beyond therapy and had discontinued corticosteroid therapy ≥ 3 weeks prior to enrolment. Whole brain radiotherapy was not allowed) 2. Prior major surgery or significant traumatic injury not fully recovered from for at least 2 weeks prior to the first dose of study treatment, or anticipation of the need for major surgery during study treatment 3. History of or known carcinomatous meningitis 4. Anticipated or on-going administration of any anticancer therapies other than those administered in this study 5. Pregnant or lactating women 6. Previous treatment with a BRAF (sorafenib allowed) or MEK inhibitor 7. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate

	Cockroft-Gault formula • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times ULN (5 times ULN for patients with concurrent liver metastases) • Bilirubin ≤ 1.5 times ULN • Alkaline phosphatase (ALP) ≤ 2.5 times ULN (5 times ULN for patients with concurrent liver metastases) 9. For premenopausal women, negative serum pregnancy test within 10 days prior to vemurafenib dosing; women of non-childbearing potential were included if they were either surgically sterile or postmenopausal for ≥ 1 year 10. For fertile men and women, the use of an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician 11. Absence of any psychological, familial, sociological, or geographical condition that would potentially hamper compliance with the study protocol and follow-up schedule; such conditions were discussed with the patient before trial entry 12. A signed informed consent form (ICF) obtained prior to study entry and prior to performing any study-related procedures	absorption (patients must have been able to swallow pills) 8. Mean corrected QT (QTc) interval ≥ 450 msec at baseline 9. NCI-CTCAE Version 4.0 grade 3 haemorrhage within 4 weeks of starting study treatment 10. Any of the following within 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, or pulmonary embolism 11. On-going cardiac dysrhythmias ≥ grade 2 (NCI-CTCAE Version 4.0) 12. Uncontrolled hypertension (>150/100 mmHg) despite optimal medical therapy 13. Pre-existing thyroid abnormality with thyroid function that could not be maintained in the normal range with medication 14. Known, clinically significant, active infection 15. History of allogeneic bone marrow transplantation or organ transplantation 16. Treatment with drugs with dysrhythmic potential including terfenadine, quinidine, procainamide, diisopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, and/or indapamide 13. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated

		with study participation or study drug administration, or may have interfered with the interpretation of study results, and which, in the investigator's judgment, would have made the patient inappropriate for entry into the study 14. Previous malignancy, except for basal cell carcinoma (BCC) or SCC of the skin, carcinoma in situ of the cervix, any curatively treated cancer from which the patient was currently disease-free, or any malignancy from which the patient had been continuously disease-free for at least 5 years (an isolated elevation of the prostate-specific antigen in the absence of prostate cancer was allowed) 15. Known infectious disease including human immunodeficiency virus (HIV) positivity or acquired immune deficiency syndrome-related illness, hepatitis B virus (HBV), or hepatitis C virus (HCV) 16. Receipt of any investigational treatment within 4 weeks of study drug start

Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table 19: BRIM 2 Patient Demographics and Baseline Characteristics (N = 132)*

Characteristic	Value (%)
Sex	
Female	51 (39)
Male	81 (61)
Race	
Caucasian	130 (98)
Hispanic	2 (2)
Age	
Median — yr	51.5
<65 yr	107 (81)
≥65 yr	25 (19)
No. of prior therapies	
1	67 (51)
2	36 (27)
≥3	29 (22)
Previous IL-2	
No	81 (61)
Yes	51 (39)
ECOG status	
0	61 (46)
1	71 (54)
Stage at diagnosis	
M1a	33 (25)
M1b	18 (14)
M1c	81 (61)

Serum LDH	
Normal	67 (51)
Elevated	65 (49)

* Unless otherwise indicated values are no. (%). ECOG denotes Eastern Cooperative Oncology Group, IL-2 interleukin-2, LDH lactate dehydrogenase.

Outcomes

Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table 20: Primary and secondary outcomes of the BRIM2

Primary outcome(s) and measures - Reliability/validity/current use in clinical practice (see Table 13**)**
The primary efficacy endpoint was ORR assessed by independent central radiologic review. The ORR was defined as the number of patients with a complete response (CR) or partial response (PR) divided by the total number of treated patients. This is expressed as a percentage. To be assigned a status of PR or CR, the change in tumour measurements had to be confirmed by ≥1 repeat tumour assessment performed sequentially ≥28 days after the criterion for response was first met. ORR was calculated with corresponding exact two-sided 95% CI using the Clopper-Pearson method.
Secondary outcome(s) and measures
• To evaluate **overall survival** (OS) (expressed in months) • To evaluate **Best Objective Response Rate (BORR)** as assessed by the investigator (expressed as %), using RECIST version 1.1 criteria for metastatic melanoma. • To evaluate duration of response as assessed by the IRC (expressed in months) • To evaluate **progression-free Survival (PFS)** as assessed by the IRC (expressed in months) • To evaluate **time to response** (TTR) as assessed by the IRC (expressed in months) • To evaluate physical symptom improvement outcome (PIO) • To evaluate the **safety** (tolerability and toxicity) profile of vemurafenib using the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.0 • To validate the **cobas® 4800 BRAF V600 Mutation Test** for the detection of the BRAFV600E mutation in DNA from formalin-fixed paraffin-embedded melanoma tissue • To further characterize the **pharmacokinetic** (PK) profile of vemurafenib • To investigate the effect of vemurafenib on the QT interval and to correlate vemurafenib exposure with these electrocardiogram (ECG) parameters

Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table 21: Summary of statistical analyses in RCTs

ClinicalTrials.gov identifier NCT01006980 Roche trial no. NO25026 (BRIM 3)	
Hypothesis objective	See below
Statistical analysis	**Primary Efficacy Analysis** For the primary analysis, the BORR by IRC assessment, an estimate of the BORR and its 95% CI was determined and the 95% CI was constructed using the Copper-Pearson method. In addition to the BORR analysis, BOR was summarized by the four RECIST 1.1 categories: CR, PR, SD, and PD as described in Section 2.5.2.2. The summary also includes a category for unevaluable (UE) patients, as assessed by the IRC. The BORR by IRC assessment was also summarized with the associated exact 95% (2-sided) CI using the Copper-Pearson method in the PP population. **Secondary Efficacy Analyses** Response assessments were compared between the IRC and investigators. Concordance in response assessments was reported as the agreement in numbers and percentages of responders (BOR of CR or PR) and non-responders, as assessed by both the IRC and investigators. Discordance in response assessments was reported as the numbers and percentages of patients whose BOR assessments were different between the IRC and investigators. When one of these assessments was missing it was considered a discordance. BORR by the investigator was summarized along with the associated exact 95% (two-sided) CI using the Copper-Pearson method. Duration of response by IRC, PFS by IRC, and OS were estimated using the Kaplan-Meier method, and the 95% CI for median time was calculated using the Brookmeyer and Crowley method. The primary analysis of the study was performed when all treated patients have been followed up for at least 6 months after the last enrolled patient received the first dose of study medication

	Analysis population The intent-to-treat (ITT) population was defined as all enrolled patients who receive at least one dose of RO5185426 and had at least one post-baseline tumour assessment. Efficacy analysis was based primarily on this population. Per-protocol (PP) population is a subpopulation of the ITT patients, excluding those patients with major protocol violations of inclusion/exclusion criteria and those with other violations affecting the efficacy assessments. Safety Population was defined as all patients who received at least one or a partial dose of study therapy will be included in the safety population. In this study, the ITT population is defined as the same as the safety population. BRAF V600E-Positive Population included ITT patients whose mutation status is confirmed by Sanger sequencing as V600E-positive, excluding other V600 mutations such as V600K, V600D, and V600R (defining the BRAF Non-V600E Mutations Population). Best overall response rate (BORR) and duration of response will be summarized for this population to assess treatment effects in the patients with confirmed V600E mutations.
Sample size, power calculation	Approximately 90 patients were planned to be enrolled to assess the efficacy and safety of vemurafenib. The sample size calculation assumed 10% of patients would not qualify for the ITT population. The sample size of 80 ITT-evaluable patients was selected to demonstrate that if the BORR was 30%, the lower boundary of the exact 95% confidence interval (CI; 2-sided) for the overall response rate was at least 20%. For example, if 24 patients responded (i.e., observed overall response rate = 30%), then the 95% CI would be 20% to 41%.

Data management & patient withdrawals	Data management responsibility was performed by Quintiles, USA. **Missing Data** For the BORR, patients who received study treatment but did not undergo a post baseline tumour assessment were counted as non-responders. For duration of response, data for patients who were lost to follow-up prior to documented progression were censored at the last tumour assessment date at which the patient was known to be progression-free prior to the data cut-off date. For PFS and PFS rate at 6 months, data for patients who did not die and had no recorded post baseline tumour assessments were censored on the date of the first dose of vemurafenib plus 1 day. Patients who died without any recorded post-baseline tumour assessments after receiving the first vemurafenib dose were considered to have a PFS event on the date of death. Data for patients who were lost to follow-up prior to documented progression were censored at the last tumour assessment date at which the patient was known to be progression-free prior to the data cut-off date. Patients who died or progressed after two or more consecutive missed visits were censored at the date of the last evaluable tumour assessment. For OS, patients without post baseline information were censored at the time of first treatment with vemurafenib plus 1 day.

Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Subgroup Analysis of BORR by IRC

BORR, as determined by IRC assessment, will also be summarized within the following subsets by calculating exact, two-sided 95% CIs using the Clopper-Pearson method.

- BORR by gender (female, male)
- BORR by age (< 60, ≥ 60)
- BORR by race
- BORR by Serum Lactate Dehydrogenase (LDH< 1.5 normal vs. LDH≥ 1.5 normal)
- BORR by ECOG performance status (0 vs. 1)
- BORR by M-stage at the time of diagnosis (M1a, M1b, M1c)
- BORR by metastatic sites (< 3, ≥3)
- BORR by prior therapy (< 2, ≥2)
- BORR by brain metastases (Yes, No)
- BORR by time since metastatic disease diagnosed
- BORR by histological subtypes (superficial spreading, ocular, lentigo maligna, acral lentiginous)
- BORR by previous IL-2 (Yes, No)
- BORR by previous ipilimumab or tremelimumab (Yes, No)

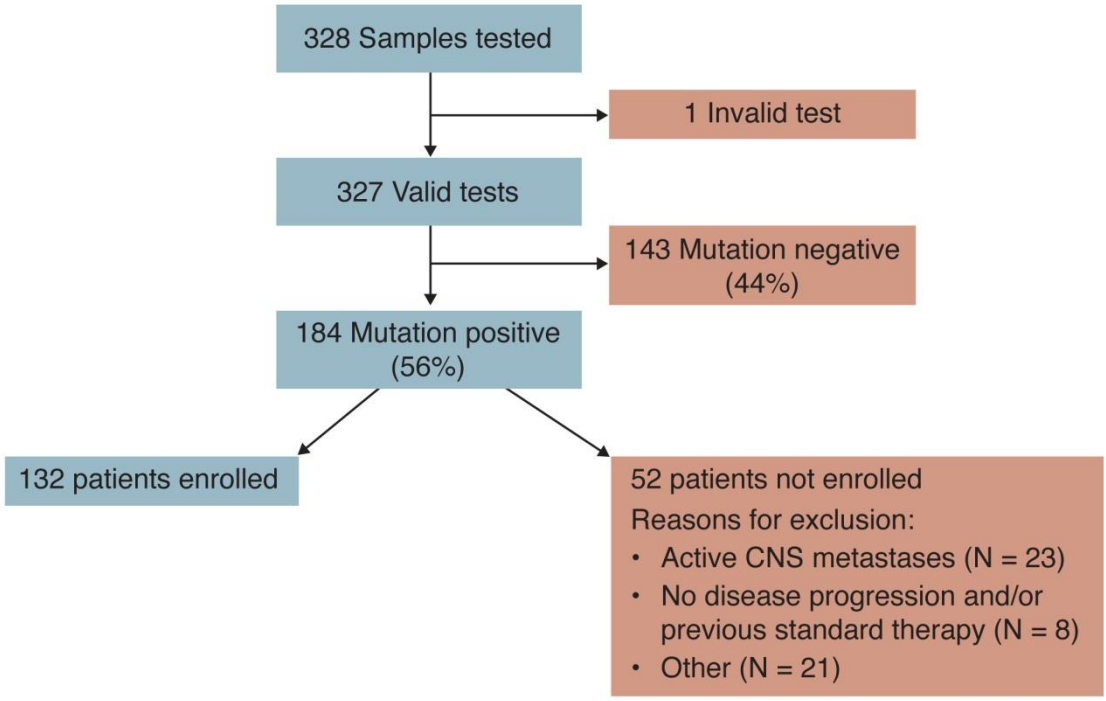
Interpretation of results will depend on sample size within each subgroup.

Disposition of Patients

Between October 2009 and March 2010, 344 patients were screened for study entry at 13 centres (10 USA, 3 Australia). Overall, 328 patients had tumour tissue tested for BRAFV600 mutations and 184 (56%) tested positive (see Figure 16). Following negative testing for BRAFV600 (N = 143), CNS metastases (N = 23) was the second most common reason for screen failure.

132 patients received the study drug and comprised the ITT population. The study was originally planned to enroll 90 patients. However, at the time the enrollment target was met, additional patients were in screening and were subsequently enrolled if determined to be eligible. At the efficacy data cut-off (July 1, 2011), median follow-up was 13 months (range 0.6 to 20.1 months). At the safety data cut-off (January 31, 2011), median follow-up was 10 months (range 0.6 to 14.7 months). The patient disposition is summarised in Figure 16)

Figure 16: BRIM2 Participant Flow and results of cobas® BRAFV600 mutation screening and enrolment of screened population*



*CNS denotes central nervous system.

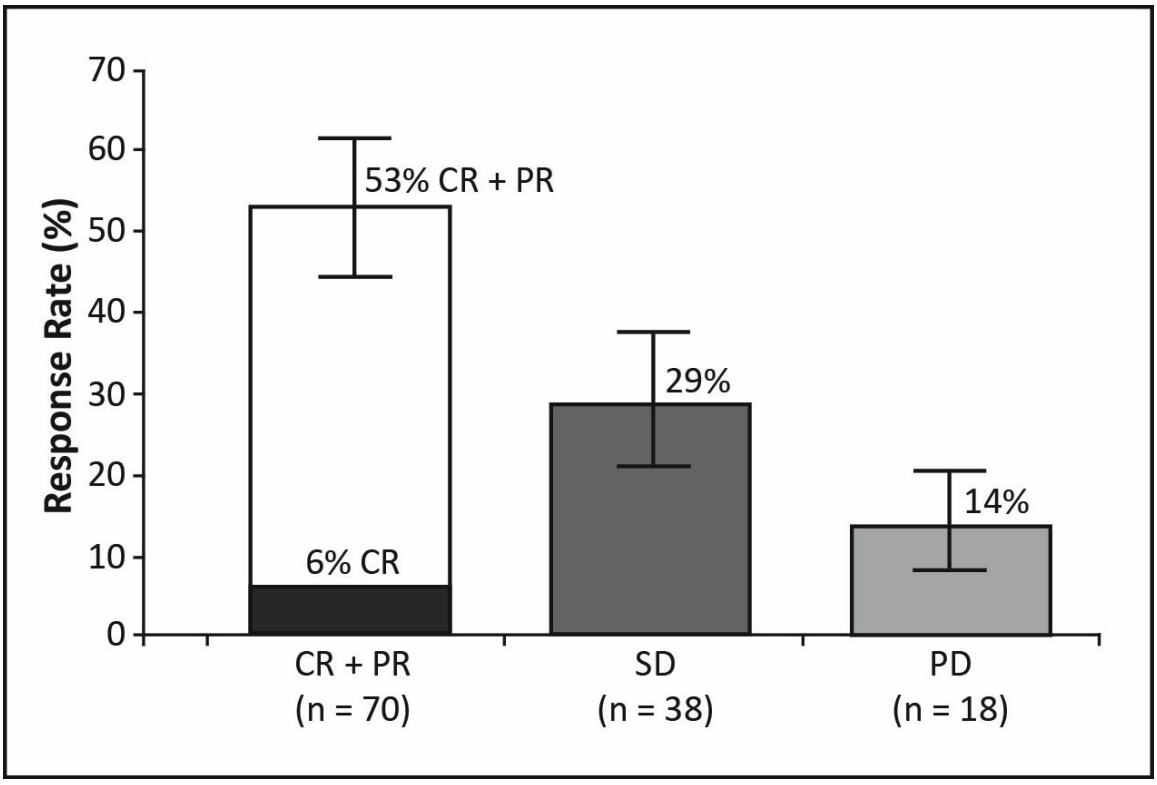
5.8.1.4 Results of the BRIM 2 (non-RCT)

5.8.1.4.1 BRIM 2: Response Rates

According to the IRC, a CR was achieved by 8 patients (6%) and a PR by 62 patients (48%), making the ORR 53% (95% CI, 44 to 62%) (see Figure 17).

The stable disease (SD) rate was 29% (N = 38; 95% CI, 21 to 37%). Seven of the responses were not recognized until after 6 months on treatment. Six patients had missing assessments or were not assessable. Only 18 patients (14%; 95% CI, 8 to 21%) had PD as their best overall response. The ORR as assessed by investigators was 57% (PR 52% and CR 5%). The IRC and investigator ORR assessments demonstrated 83% concordance. Among predefined subgroups of significant size (>25 patients), all had an ORR >30%, the protocol target rate.

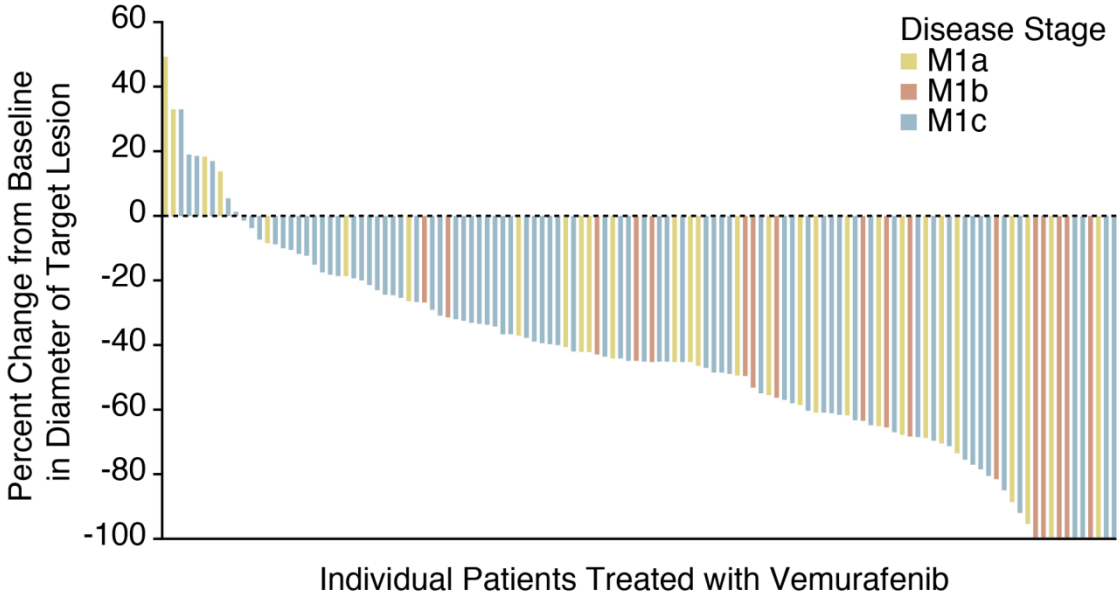
Figure 17: BRIM2 Overall Response Rate (ORR) in previously treated patients with BRAFV600 mutant metastatic melanoma received vemurafenib 960 mg orally twice daily (with 95% confidence intervals), as assessed by independent review committee*



* Six patients (5%) had missing/unavailable data. CR denotes complete response, PD, progressive disease, PR, partial response, and SD, stable disease.

Figure 18: Objective tumour responses with vemurafenib by metastatic stage*. Measured as the percentage change from baseline in the sum of

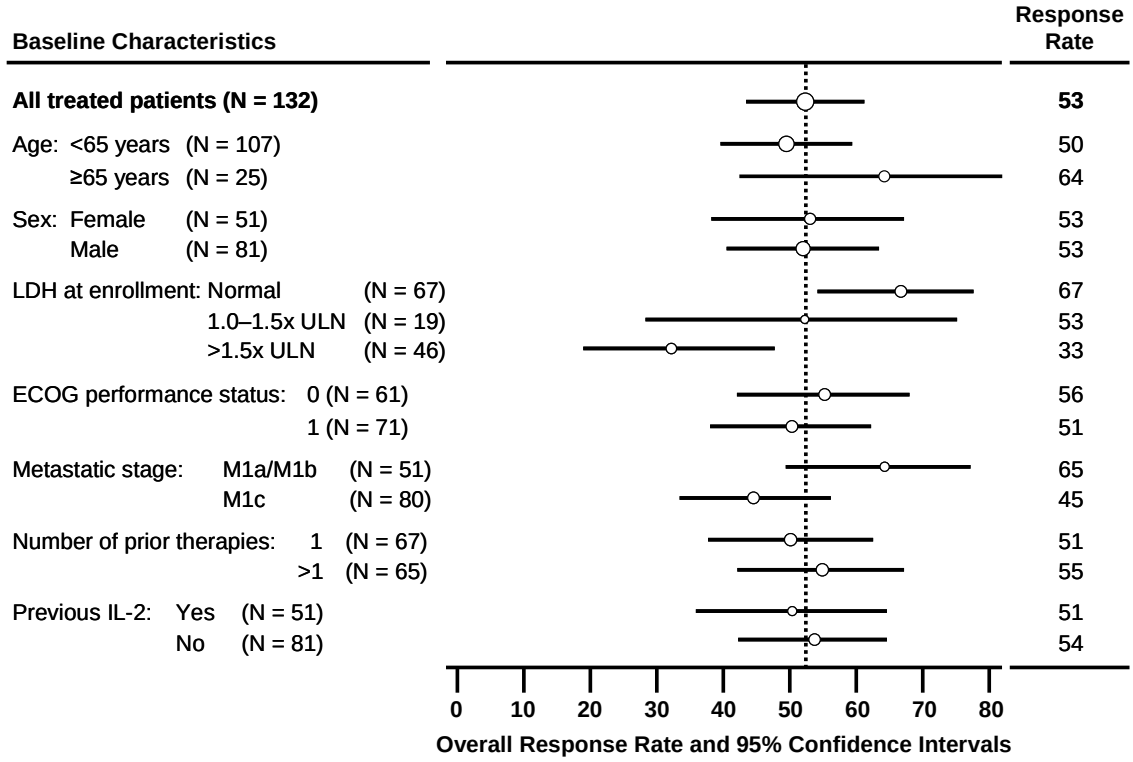
the largest diameter of each target lesion. Negative values indicate tumour shrinkage.



* Ten patients had 100% reduction in target lesions; 2 of the 10 patients had non-target lesions and were therefore partial responders; there were thus 8 complete responders defined by Response Evaluation Criteria in Solid Tumours. One patient was assessed as a partial responder after the development of on-study progressive disease.

Compared with the ORR of the total population, the ORR of the subgroups defined by key prognostic factors (e.g., LDH, ECOG performance status, and stage) were generally consistent, except those with LDH >1.5 times the upper limit of normal (ULN), who had an ORR of 33% (95%CI, 19 to 48%; 46 patients) (see Figure 19).

Figure 19: BRIM2 Overall response rates and 95% confidence intervals in patient subgroups defined by baseline demographic or disease characteristics*



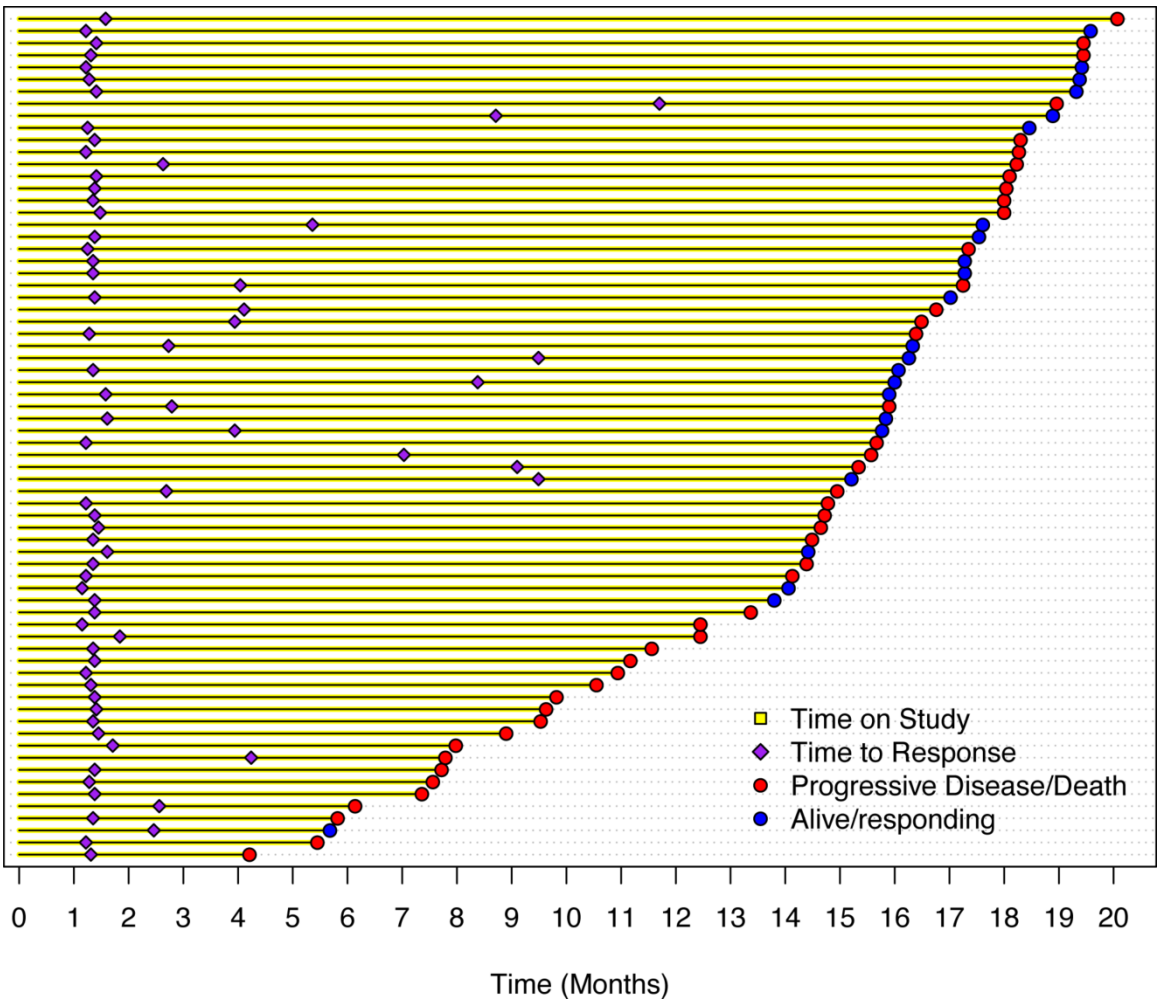
* Vertical dashed line represents the overall response rate of the total study population. O represents the response rate for each subset; represents the 95% confidence interval for each subset. ECOG denotes Eastern Cooperative Oncology Group, IL-2, interleukin-2, LDH, lactate dehydrogenase, ULN, upper limit of normal.

Among the 10 patients with BRAF V600K mutations, there were 4 PRs, 3 with SD, 2 with PD, and 1 who was unevaluable.

In the 70 responding patients, 41 have progressed, 26 had died, and 23 were progression-free at the data cut-off (July 1, 2011). All but one of the 23 patients carried a continued response beyond 12 months since initiating vemurafenib (31% of responders and 17% of the intent-to-treat population). One patient considered a PR by IRC assessment after an investigator-determined PD was excluded from the duration of response analysis. The

median duration of response was 6.7 months (95% CI, 5.5 to 9.6) with a range of 1.6 to 18.1 months. Thirty-three patients (25% of the 132 patients), including those with SD, remained progression-free at the time of data cut-off (see Figure 20).

Figure 20: BRIM2 Time to response and time of progression by individual patients who responded to treatment (n = 69).

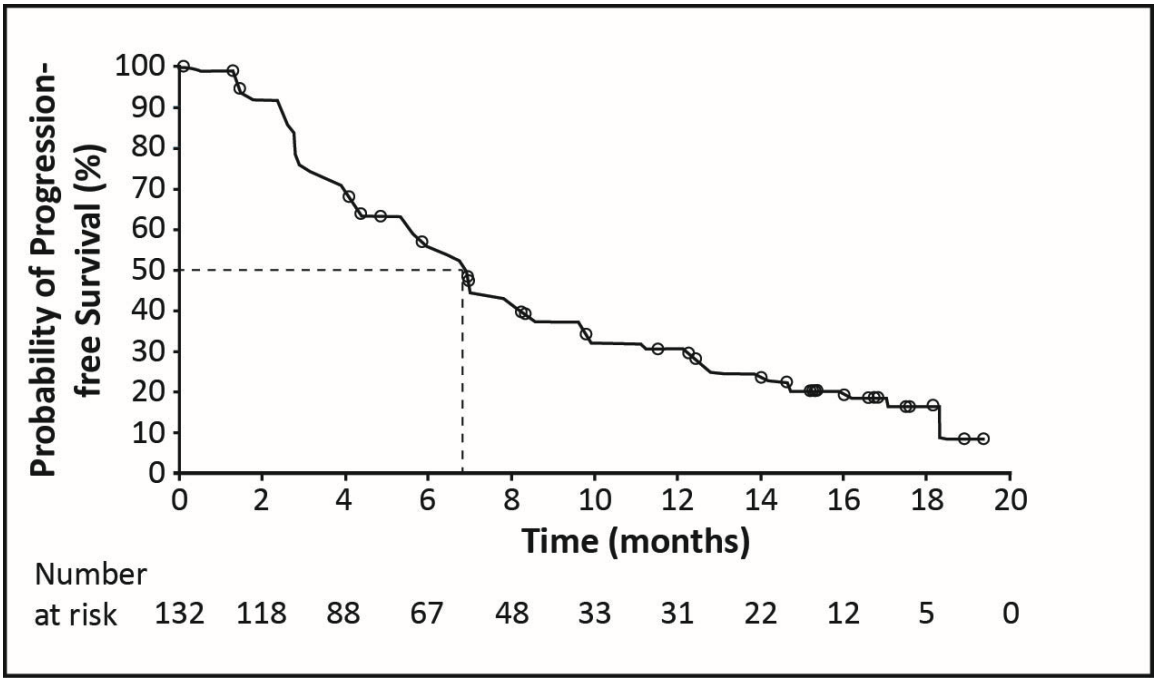


Shows months on study and intervals to confirmed response and progressive disease or death.

5.8.1.4.2 BRIM 2: Progression-Free Survival

PFS ranged from 0.0 to 19.4 months (see Figure 21), with a median duration of 6.8 months (95% CI, 5.6 to 7.6months). The 6-month PFS rate was 54% (95% CI, 43 to 68%).

Figure 21: BRIM2 Kaplan–Meier estimate for the probability of Progression-Free Survival in all patients who received vemurafenib*

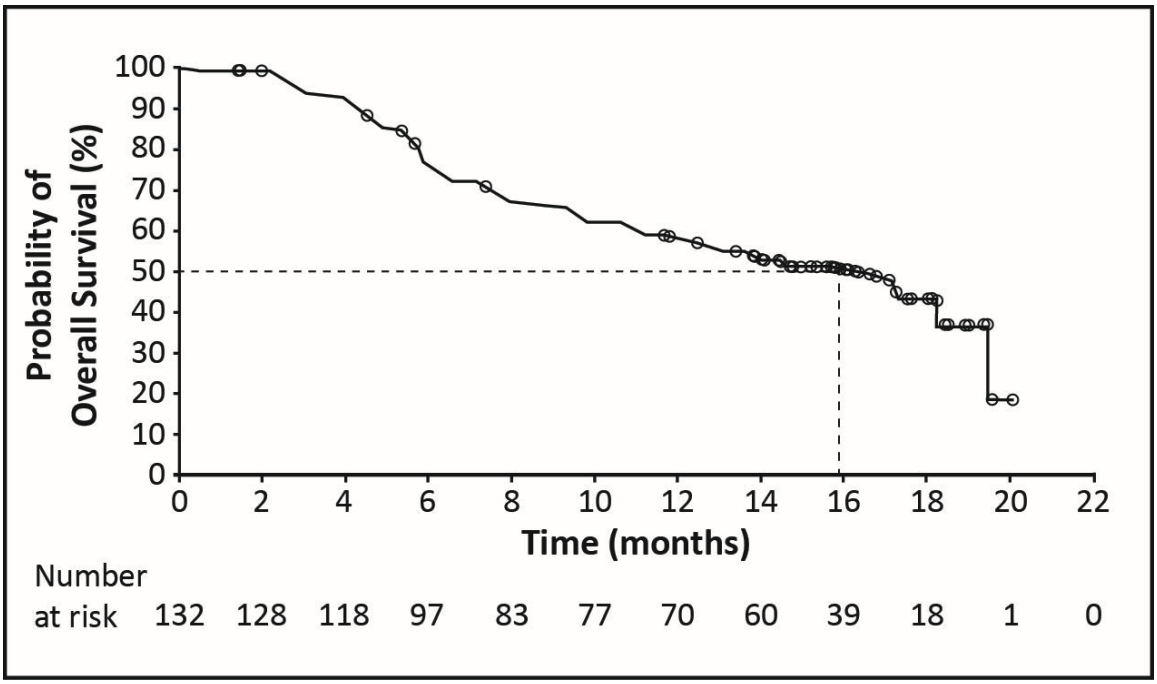


*Open circles represent the date of last evaluable tumour assessment before data cut-off in censored patients without disease progression or death.

5.8.1.4.3 BRIM 2: Overall Survival

Of the 132 patients enrolled in the study, 62 (47%) were alive as of July 1, 2011, and the median OS was 15.9 months (95% C.I 11.6-18.3) with a range of 0.6 to 20.1 months (see Figure 22). The OS rate at 6 months was 77% (95% CI, 70 to 85%), 65% at 9 months (95% CI, 57 to 74%), 58% at 12 months (95% CI, 49 to 67%) and estimated to be 43% at 18 months (95% CI 32.6 to 52.8%]. During the period of follow up, 32 patients (24%) received ipilimumab following progression on vemurafenib.

Figure 22: BRIM2 Kaplan–Meier estimate for the probability of Overall Survival in all patients who received vemurafenib*



*Open circles represent the date of last evaluable tumour assessment before data cut-off in censored patients without disease progression or death.

5.9 Adverse events

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

Not applicable.

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

5.8.3.1 BRIM 3 Safety (data cut-off date December 30, 2010)

A total of 618 patients (92%) underwent at least one assessment as of the clinical cut-off date and were evaluated for toxic effects. Adverse events of grade 2 or more that were reported in more than 5% of the patients in either study group are shown in Table 22. It should be noted in any comparison of adverse event rates between the two study arms that treatment duration in the vemurafenib arm is substantially longer than in the dacarbazine arm (3.1

months in the vemurafenib group versus 0.76 months in the dacarbazine group (time from first to last of the infusions given once every 3 weeks) so that treatment-related adverse events are more likely to be recorded for vemurafenib. This may also be demonstrated by the fact that more patients receiving vemurafenib stayed on treatment compared to those receiving dacarbazine (223 patients (66.4%) in the vemurafenib arm versus83 patients (28.7%) in the dacarbazine arm).

The most common adverse events in the vemurafenib group were cutaneous events, arthralgia, and fatigue; photosensitivity skin reactions of grade 2 or 3 were seen in 12% of the patients, with grade 3 reactions characterized by blistering that often could be prevented with sunblock. As expected, the most common severe toxic effects in the dacarbazine group were fatigue, nausea, vomiting, and neutropenia. Adverse events led to dose modification or interruption in 129 of 336 patients (38%) in the vemurafenib group and in 44 of 282 patients (16%) in the dacarbazine group.

In the vemurafenib group, a cutaneous squamous-cell carcinoma, keratoacanthoma, or both developed in 61 patients (18%). All lesions were treated by simple excision.

Table 22: BRIM 2 Adverse Events Occurring in ≥ 5% of Patients in Either Treatment Group (Safety Population)

Body System/ Adverse Event	**dacarbazine n = 282 No. (%)**	**vemurafenib n = 336 No. (%)**
All Body Systems		
Total Pts With At Least One AE	253 (90)	326 (97)
Total Number Of AEs	1274	3469
Gastrointestinal Disorders		
Total Pts With At Least One AE	182 (65)	213 (63)
Nausea	115 (41)	101 (30)
Diarrhoea	34 (12)	84 (25)
Vomiting	67 (24)	50 (15)
Constipation	65 (23)	32 (10)

Abdominal Pain	12 (4)	19 (6)
Abdominal Pain Upper	5 (2)	23 (7)
Skin And Subcutaneous Tissue Disorders		
Total Pts With At Least One AE	53 (19)	302 (90)
Rash	3 (1)	121 (36)
Alopecia	6 (2)	117 (35)
Photosensitivity Reaction	10 (4)	101 (30)
Pruritus	4 (1)	74 (22)
Hyperkeratosis	-	67 (20)
Dry Skin	3 (1)	54 (16)
Erythema	4 (1)	38 (11)
Actinic Keratosis	9 (3)	21 (6)
Rash Maculo-Papular	1 (<1)	29 (9)
Palmar-Plantar Erythro-	1 (<1)	22 (7)
Dysaesthesia Syndrome	1 (<1)	21 (6)
Skin Lesion	-	17 (5)
Keratosis Pilaris		
General Disorders And Administration Site Conditions		
Total Pts With At Least One AE		
Fatigue	142 (50)	213 (63)
Pyrexia	87 (31)	112 (33)
Oedema Peripheral	25 (9)	59 (18)
Asthenia	13 (5)	50 (15)
Pain	22 (8)	28 (8)
Chills	14 (5)	22 (7)
	3 (1)	17 (5)
Musculoskeletal And Connective Tissue Disorders		
Total Pts With At Least One AE		
Arthralgia	67 (24)	225 (67)
Pain In Extremity	9 (3)	165 (49)
Myalgia	17 (6)	45 (13)
Back Pain	4 (1)	39 (12)
Musculoskeletal Pain	13 (5)	20 (6)
	9 (3)	21 (6)
Nervous System Disorders		
Total Pts With At Least One AE	67 (24)	152 (45)
Headache	26 (9)	72 (21)
Dysgeusia	9 (3)	44 (13)
Dizziness	10 (4)	20 (6)
Paraesthesia	13 (5)	15 (4)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)		
Total Pts With At Least One AE		
Skin Papilloma	25 (9)	144 (43)
Squamous Cell Carcinoma Of Skin	-	62 (18)
Keratoacanthoma Seborrhoeic		

Keratosis	1 (<1) - 3 (1)	40 (12) 27 (8) 24 (7)
Infections And Infestations Total Pts With At Least One AE Nasopharyngitis	 49 (17) 9 (3)	 101 (30) 17 (5)
Investigations Total Pts With At Least One AE Weight Decreased Blood Alkaline Phosphatase Increased Alanine Aminotransferase	 37 (13) 6 (2) - 3 (1)	 93 (28) 20 (6) 25 (7) 18 (5)
Increased Respiratory, Thoracic And Mediastinal Disorders Total Pts With At Least One AE Cough Dyspnoea	 53 (19) 16 (6) 20 (7)	 74 (22) 23 (7) 19 (6)
Metabolism And Nutrition Disorders Total Pts With At Least One AE Decreased Appetite	 33 (12) 20 (7)	 74 (22) 53 (16)
Blood And Lymphatic System Disorders Total Pts With At Least One AE Neutropenia Anaemia Thrombocytopenia	 51 (18) 32 (11) 15 (5) 14 (5)	 32 (10) 2 (<1) 17 (5) 4 (1)
Psychiatric Disorders Total Pts With At Least One AE Insomnia	 28 (10) 12 (4)	 51 (15) 19 (6)
Injury, Poisoning And Procedural Complications Total Pts With At Least One AE Sunburn	 14 (5) -	 52 (15) 31 (9)

The overall incidence of Grade 4 (life-threatening) AEs was lower in the vemurafenib group (13 patients [4%] with 14 AEs) than the dacarbazine group (22 patients [8%] with 27 AEs). Grade 4 AEs in the vemurafenib group included: pulmonary embolism (3 patients), increased GGT (2 patients), increased blood creatinine phosphokinase (CPK), increased blood bilirubin, increased lipase, ageusia, intraventricular haemorrhage, pneumonia, pneumothorax, respiratory distress, neutropenia (all 1 patient each). As of the clinical cut-off, five vemurafenib patients had a total of six Grade 4 AEs that were considered by the investigator to be related to treatment:

• Three of the drug-related Grade 4 AEs in the vemurafenib group were elevations in LFTs (one patient with recurrent elevation in total bilirubin associated with elevated alkaline phosphatase and ALT which led to drug discontinuation. Two patients had Grade 4 GGT increase without concomitant total bilirubin).

• Other drug-related Grade 4 AEs included neutropenia, ageusia, and increased CPK, which all resolved with dose modification on study. Grade 4 increased lipase was reported before the clinical cut-off date with no defined relationship to study treatment; however, after the cut-off, it was defined by the investigator as related to treatment with vemurafenib.

Grade 4 AEs unrelated to treatment included pulmonary embolism, intraventricular haemorrhage, respiratory distress, pneumothorax, and pneumonia which may be related to the underlying cancer.

In the dacarbazine group, Grade 4 AEs were mostly haematological included: neutropenia (8 patients), decreased neutrophil count (5 patients), thrombocytopenia (2 patients), dyspnoea (2 patients), pulmonary embolism and thrombosis (in same patient), decreased platelet count, hypercalcaemia, hyponatremia, hyperuricemia, lower abdominal pain, pleural effusion, deep vein thrombosis, atrial fibrillation (1 patient each). Of these Grade 4 AEs, all cases of neutropenia/decreased neutrophil count were considered drug related by the investigator. Other drug-related Grade 4 AEs in the dacarbazine group included: thrombocytopenia/platelet count decreased (3 patients), deep vein thrombosis (1 patient), and pulmonary embolism (1 patient).

Table 23: BRIM 2 Adverse Events of Grade 3, 4, 5 Occurring in ≥ 2% of Patients in Either Treatment Group (Safety Population)

Body System/ Adverse Event	**dacarbazine** **n = 282**	**Vemurafenib** **n = 336**

	No. (%)	No. (%)
All Body Systems Total Pts with at Least one AE Total Number of AEs	 86 (30) 144	 168 (50) 308
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps) Squamous Cell Carcinoma Of Skin Keratoacanthoma	 1 (<1) -	 38 (11) 20 (6)
Skin And Subcutaneous Tissue Disorders Rash Photosensitivity Reaction Rash Maculo-Papular	 - - -	 28 (8) 9 (3) 8 (2)
Investigations Neutrophil Count Decreased Increased Gamma-Glutamyltransferase Increased Blood Alkaline Phosphatase	 10 (4) - -	 - 9 (3) 7 (2)
Increased Blood And Lymphatic System Disorders Neutropenia Thrombocytopenia	 24 (9) 6 (2)	 1 (<1) 2 (<1)
General Disorders And Administration Site Conditions Fatigue	 5 (2)	 6 (2)
Gastrointestinal Disorders Nausea	 5 (2)	 4 (1)
Musculoskeletal And Connective Tissue Disorders Arthralgia	 2 (<1)	 11 (3)
Respiratory, Thoracic And Mediastinal Disorders Dyspnoea	 8 (3)	 2 (<1)

Adverse Events Leading to Death (Grade 5 AEs)

The overall incidence of AEs with outcome of death (Grade 5 AEs) was the same in both treatment groups (6 patients [2%]) (see Table 24).

Deaths

As of the initial cut-off date, a total of 42 patients (13%) in the vemurafenib group had died during the course of the study (see Table 24), and 22 of these

patients (6.5%) died within 28 days of their last RO5185426 dose. In the dacarbazine group, a total of 66 patients (23%) died during the study; 16 (5.5%) within 28 days of the last dacarbazine dose. The overwhelming majority of deaths in both treatment arms were attributable to disease progression

Table 24: BRIM 3 Summary of Deaths by Primary Cause (All Treated Patients)

Primary cause of death	**dacarbazine** **n = 289** **No. (%)**	**Vemurafenib** **n = 336** **No. (%)**
Total No. of Deaths	66 (23)	42 (13)
Disease Progression	63 (22)	35 (10)
Other	2 (<1)	3 (<1)
Adverse Events	1 (<1)	2 (<1)
Unknown	-	2 (<1)

Impact of Safety Profile on Patients

As expected, due to the differing mechanisms of action, the nature of the safety profiles of vemurafenib and dacarbazine are different. Therefore it is helpful to take a broad view of the impact of toxicity on patients as well as comparing the frequency of specific adverse events, as is done in Table 25. In summary:

- The most common adverse events in the vemurafenib group were cutaneous events, arthralgia, and fatigue; photosensitivity skin reactions of grade 2 or 3 were seen in 12% of the patients, with grade 3 reactions characterized by blistering that often could be prevented with sunblock. Cutaneous squamous-cell carcinoma, keratoacanthoma, or both developed in 61 patients (18%) and were removed by local exicision.

- The most common severe toxic effects in the dacarbazine group were fatigue, nausea, vomiting, and haematological toxicities including neutropenia and subsequent infection.

- Adverse events led to dose modification or interruption in

    - 129 of 336 patients (38%) in the vemurafenib group
    - in 44 of 282 patients (16%) in the dacarbazine group

- It should be noted that dose reduction is much more likely with a chronic oral treatment given over many months than with cyclical chemotherapy given every 3 weeks for a few cycles. The higher levels of dose reduction with vemurafenib should not be taken as indicating an inherently less well tolerated drug

Table 25: BRIM 3 Overview of Adverse Events and Deaths (Safety Population)

Adverse Events	**dacarbazine n = 282**	**vemurafenib n = 336**
	Number (%) of Patients	Number (%) of Patients
Any AEs	253 (90)	326 (97)
AEs of Grade 3 and above	86 (30)	168 (50)
AEs of Grade 3	74 (26)	163 (49)
AEs of Grade 4	22 (8)	13 (4)
AEs of Grade 5	6 (2)	6 (2)
Deaths †	66* (23)	42* (13)
Deaths within 28 days of last dose of study drug†	16 (5.5)	22 (6.5)
Serious AEs	45 (16)	110 (33)
Drug-related AEs	194 (69)	316 (94)
Drug-related serious AEs		
AEs that led to discontinuation	15 (5)	88 (26)
AEs that led to dose modification/interruption	12 (4)	19 (6)

* 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.

Dose modification in BRIM 3

Although dose-reductions and interruptions were fairly common with vemurafenib, treatment discontinuation was not very common, indicating that the flexibility of twice daily dosing on a continuous basis allows fine tuning to manage side-effects (See Table 26)

Table 26: Summary of Dose Modification (Reduction or Interruption) in BRIM 3

	vemurafenib n = 336 No. (%)	dacarbazine n = 289 No. (%)
Patients with at least one dose modification (reduction or interruption) No.(%)	159(47.3)	44 (15.2)
Dose modification Reasons:		
Dose adjusted per protocol*	92(27.4)	-
Non-compliance	26(7.7)	-
Other**	136(40.5)	13 (4.5)
Adverse Event	-	25 (8.7)
Patients with at least one dose reduction No.(%)	112(33.3)	44 (15.2)
Number of dose reductions/patient		
Mean	1	1
SD	0.6	0.7
Median	1	1
25% and 75%-ile	1-2	1-1
Min,Max	1-5	1-4
Last prescribed total daily doses for patients with dose reduction (mg per day)		
n	112(33.3)	n/a
1680 mg	1(0.3)	n/a
1440 mg	83(24.7)	n/a
1200 mg	1(0.3)	n/a
960 mg	26(7.7)	n/a
480 mg	1(0.3)	n/a
Patients with ≥one dose interruption No.(%)	147(43.8)	5 (1.7)***
Number of dose interruptions per patient		5 (1.7)
Mean	2	1
SD	1.1	0.4
Median	1	1
25% and 75%-ile	1-2	1-1
Min, Max	1-6	1-2

Duration of Maximum Dose Interruptions per patient (days)		
Mean	8	n/a
SD	6.2	n/a
Median	7	n/a
25% and 75%-ile	4-12	n/a
Min,Max	1-38	n/a
<1 Week	67(19.9)	n/a
>=1 Week	80(23.8)	n/a

* Per-protocol: Dose modification for safety reasons.
** 80% of the reasons coded as "other" were because of an AE. The other 20% were a mixture of reasons (including: missed dose, held dose, forgot to take drug, ran out of drug, drug holiday, progressive disease, patient decision, etc).
*** Dose interruption is defined as missing cycles

BRIM2 SAFETY (data cut-off date January 31, 2011)

The findings with respect to safety were consistent with BRIM 3.

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The safety data of BRIM 3 shows that treatment with vemurafenib may result in some adverse events which are generally manageable and do not generally require admission to hospital. When put in the context of rapid tumour shrinkage response (median time to response 1.45 months), it is more than likely that symptomatic aggressive disease can be quickly palliated with the trade-off of exposing patients to adverse events that do not usually require extensive medical care. Furthermore, the ability to modify the dose of vemurafenib allows the management of adverse events.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

At 6 months, overall survival was 84% (95% confidence interval [CI], 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine

group. In the interim analysis for overall survival and final analysis for progression-free survival, vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with dacarbazine (P<0.001 for both comparisons). Response rates were 48% for vemurafenib and 5% for dacarbazine. After review of the interim analysis by an independent data and safety monitoring board, crossover from dacarbazine to vemurafenib was recommended.

Despite the cross-over of patients from the dacarbazine arm to the vemurafenib arm following the interim analysis, the updated analysis of the BRIM 3 data has shown that the 6 month survival rates for vemurafenib have been maintained compared to dacarbazine, although the relative risk of reduction increased from 0.37 (95% CI; 0.26 - 0.55) to 0.44 (95% CI; 0.33 - 0.59). The most recent data cut (3rd October 2011) has showed the median overall survival for the vemurafenib treatment group had been reached, with a median OS of 13.2 months (see Figure 13). At this stage, the median OS for the dacarbazine arm was 9.6 months. The hazard ratio was 0.62 (95% CI 0.49-0.77).

As expected, due to the differing mechanisms of action, the nature of the safety profiles of vemurafenib and dacarbazine are different. Therefore it is helpful to take a broad view of the impact of toxicity on patients as well as comparing the frequency of specific adverse events, as is done in Table 25. In summary:

- The most common adverse events in the vemurafenib group were cutaneous events, arthralgia, and fatigue; photosensitivity skin reactions of grade 2 or 3 were seen in 12% of the patients, with grade 3 reactions characterized by photosensitivity that often could be prevented with sunblock.

- The most common severe toxic effects in the dacarbazine group were fatigue, nausea, vomiting, and neutropenia.

- Adverse events led to dose modification or interruption in

    - 129 of 336 patients (38%) in the vemurafenib group
    - in 44 of 282 patients (16%) in the dacarbazine group

- In the vemurafenib group, a cutaneous squamous-cell carcinoma, keratoacanthoma, or both developed in 61 patients (18%).

    - All lesions were treated by simple excision

Vemurafenib produced improved rates of overall and progression-free survival in patients with previously untreated melanoma with the BRAF V600E mutation, while delivering a manageable safety profile.

The results achieved with vemurafenib are of immense significance and relevance to patients. It improved median survival by 3.6 months (38%) and reduces the risk of death by 38% compared with dacarbazine, the chemotherapy agent that has been the standard treatment in this condition for 30 years, despite never demonstrating any ability to improve OS in a randomised trial. Other efficacy measures such as progression-free survival and response rate were also dramatically improved. Of note, most of the patients in the vemurafenib group experienced some degree of tumour shrinkage indicating that there are few patients who are currently taking vemurafenib without experiencing some degree of benefit, either if they are previously untreated (see Figure 7) or have progressed on previous lines of therapy (see Figure 18). Moreover responses tend to be rapid (median time to response 1.45 months) making it possible to identify early patients who are not benefitting so that fruitless treatment can be stopped. Although dose adjustments are relatively common during vemurafenib therapy, these are

easy to carry out given the vemurafenib dose schedule so that dosing can be tailored to patient needs. This, as well as its intrinsic tolerability profile may explain why only 4% of patients on vemurafenib experienced Grade 4 adverse events compared with 8% on dacarbazine, despite the much longer treatment duration of patients receiving vemurafenib. In summary, when faced with very few treatment options in readily identifiable metastatic melanoma patients, the data supporting vemurafenib provides a compelling case as a treatment option.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The strengths and limitations for the clinical evidence supporting vemurafenib are outlined in

Table 27.

Table 27: Summary of the strengths and limitations of the clinical-evidence base for vemurafenib

Strengths of clinical evidence base	**Weaknesses of clinical evidence base**
Randomised control study showing improved response rates, time to response, progression-free survival and overall survival with vemurafenib compared to the current standard of care, dacarbazine.	This was an open label study, and there was no double dummy blinding, but the primary end-point of OS is an objective one making this less important.
Despite limited follow-up, the response rates and time to response are improved in patients receiving vemurafenib compared to those taking the current standard of care,	The analysis of the data was expedited for regulatory reasons, resulting in limited follow-up at the initial data-cut. However updated analyses have shown improved

dacarbazine.	overall survival with vemurafenib compared to the current standard of care, dacarbazine.
The metastatic melanoma population is small when compared to other tumour types such as breast, lung or colorectal cancer. Therefore, it should not be expected that multiple studies can be recruited for in any pragmatic manner. Despite being a single study, it has been conducted in a robust and swift manner, delivering the results outlined in this submission, and offering a treatment option for an area of unmet need. These results are consistent with the high level of activity seen in the Phase 2 study BRIM 2	Data has only been shown in a single RCT.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The current standard of care for metastatic melanoma, dacarbazine, has historically resulted in overall survival, progression-free survival and response rates that do not compare favourably to vemurafenib. The BRIM 3 study provides evidence of improved outcomes which are within the scope of this appraisal when compared to the current standard of care in the UK, dacarbazine, with a sufficiently powered study to show overall survival and

progression-free survival. Fourteen UK centres took part in this study, recruiting over 10 percent of the patients.

Currently, the treatment options for previously untreated metastatic melanoma patients are limited, offering low response rates, particularly in light of a disease that is acknowledged to be generally aggressive. Therefore BRIM 3 represents the most relevant evidence base when considering the use of a chemotherapy in previously untreated metastatic melanoma patients, with the BRAF V600E mutation, in the UK

The primary and secondary outcomes have been well established in oncology, and have been utilised in the development for existing licensed therapies. These outcomes are familiar to oncologists, and are relevant to patients with metastatic melanoma.

Vemurafenib is licensed for patients with previously untreated melanoma with the BRAF V600 mutation. Patients can be readily identified by means of a clinically validated test, the cobas® 4800 BRAF V600 Mutation Test, as used in BRIM3 and BRIM2.

Where assistance with BRAF testing is sought by clinicians to support the treatment of patients with metastatic melanoma, Roche Products Ltd is offering to fund such testing using the cobas® 4800 BRAF V600 Mutation Test at one of three UK laboratories that are collaborating with Roche. The collaborative laboratories are Institute of Cancer Research, Surrey; Queen Elizabeth Hospital, Birmingham; and Saint Mary's Hospital, Manchester.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the

evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

None identified.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

Embase (EMYY), Embase Alert, (EMBA), Medline (MEYY), EconLIT and NHS EED were searched for studies assessing the cost-effectiveness of vemurafenib. The search was designed to evaluate whether de novo modelling was necessary in order to answer the decision problem. Since a full systematic review of cost-effectiveness studies in melanoma was conducted in support of the ongoing NICE technology appraisal for ipilimumab, this searched focused only on new studies and papers since December 9th 2010 (the date on which systematic review for ipilimumab was carried out). The complete search strategy is provided in section 9.10. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Keyword strategies were developed using key references retrieved through initial scoping searches. The search was limited by dates after the 9th December 2010. ProQuest was used to search EMYY, EMBA and MEYY on 17th January 2012 whilst NHS EED was searched using The Centre for Reviews and Dissemination's website (University of York 2011) and Econ LIT was searched (The American Economic Association & EconLIT 2011), both accessed on 19th December 2012. Each search result's title and abstract

were assessed for relevance according to the pre-defined inclusion and exclusion criteria. If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

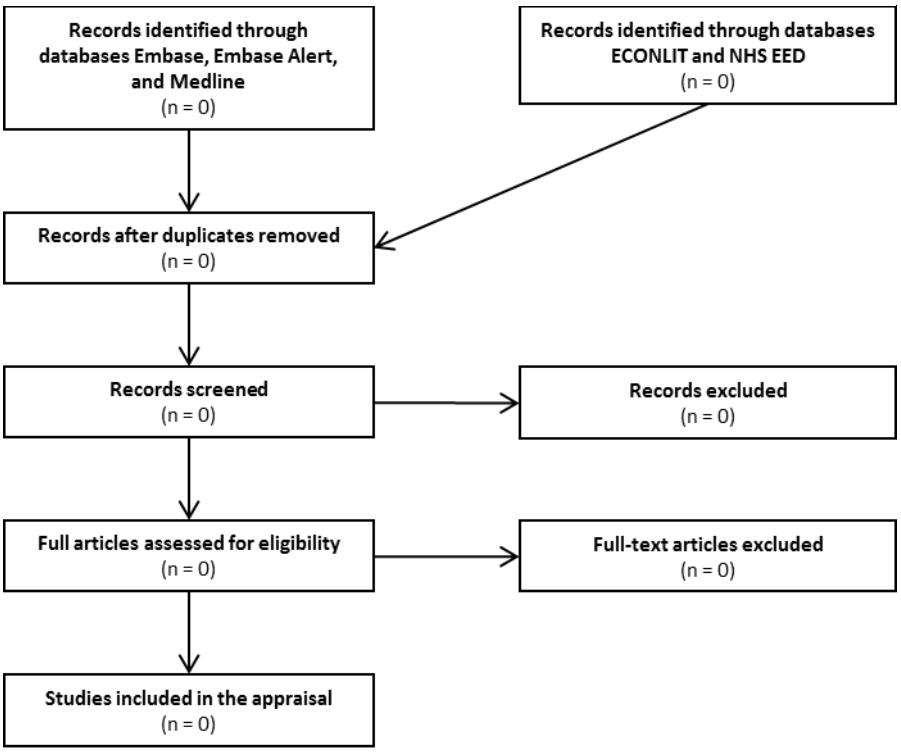
Table 28: Inclusion and Exclusion criteria for cost-effectiveness studies

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 Evaluations (cost effectiveness analyses, cost utility analyses, cost minimisation analyses)	RCTs, Observational Data, Budget Impact Assessments

The above methodology is founded on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008). The objectives of the search, and the inclusion criteria and exclusion criteria defined as a product of those objectives, were clearly aligned with the decision problem.

No cost-effectiveness studies of vemurafenib were identified.

Figure 23: PRISMA Flow showing economic studies identified through searching of the databases



Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Not applicable. No studies identified.

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated

instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

Not applicable. No studies identified.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The de novo economic model constructed was designed 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.

In addition to first-line the scope of this appraisal also specifies that the cost-effectiveness of vemurafenib as a second line treatment for BRAF V600 mutation positive melanoma should be assessed. Due to a lack of randomised controlled data in this setting and an absence of data on the outcomes experienced by previously treated BRAF V600 mutation positive patients untreated with vemurafenib this analysis is somewhat more problematic (as

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

the incremental QALY gain associated with vemurafenib in this setting and resultant ICER cannot be robustly estimated).

When the absence of RCT or historical control data in the second line setting is considered in light of:

- the magnitude of the ICERs estimated in the first line model (£94,267/QALY in the base-case and potentially higher if using alternative extrapolation),
- the high degree of uncertainty associated with the first line model presented (due to the immaturity of the data available in BRAF V600 mutation positive patients relative to the wealth of other data available in a general melanoma population)
- the expectation that the cost-effectiveness of vemurafenib in first line and second line are unlikely to differ significantly (due in part to the relatively short amount of time between first and second line treatment in metastatic melanoma)

we believe it is not possible to robustly demonstrate that vemurafenib is a cost-effective use of NHS resources in the second line treatment of melanoma.

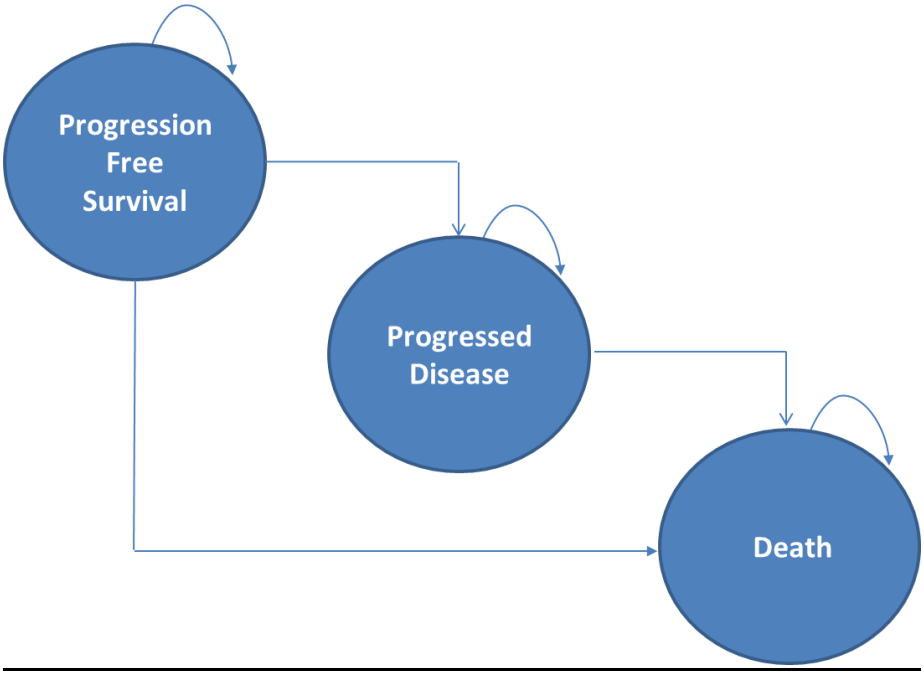
Due to this we have not attempted to derive specific ICERs on the use of vemurafenib in a second line setting or to build a decision analytic model. If a model were to have been constructed in this setting it would have been subject to even more uncertain that the (already highly uncertain) first line model which demonstrates clearly that the ICER associated with vemurafenib is unlikely to be in the range typically considered acceptable in NICE appraisals.

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

During the development of the de novo economic model an advisory board was held with clinical experts experienced in the treatment of melanoma and in the use of vemurafenib. These clinicians were presented with a 3 state model (progression free survival (PFS), progressed disease (PD) and death) schematic (see Figure 24 below) and asked whether they believed it was an appropriate design for modeling the decision problem.

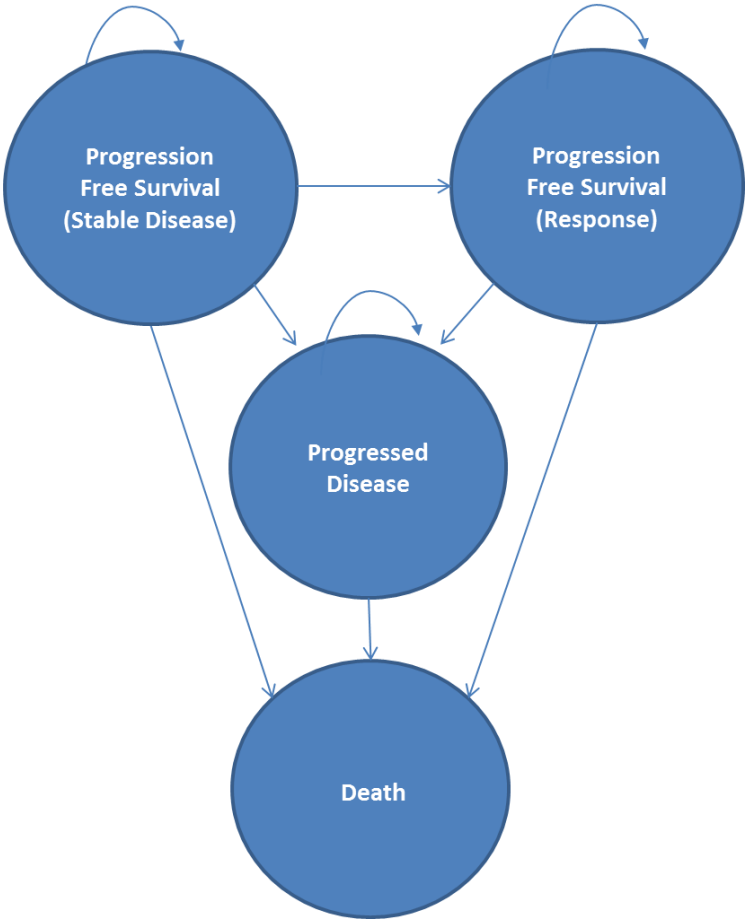
Figure 24: 3 state model schematic



These clinicians noted that one of the things they found most impressive about vemurafenib was its ability to induce an extremely quick response in a high number of patients. They noted that the response rate for vemurafenib in BRIM3 (48.4%) was approximately 9 times that observed for dacarbazine (5.5%) and over 4 times higher than that observed for ipilimumab monotherapy in the Hodi RCT (11%). They stated that the difference they see in their patients when responding to vemurafenib is so substantial that it appears inappropriate to use a single PFS health state without considering the sizeable benefit that this rapid and highly likely response offers.

In response to this it was suggested that three state approach could be extended to include two different PFS health states; one for patients responding to treatment and one for patient with stable disease. Following this discussion the following model structure was proposed:

Figure 25: 4-state model design considered



The above model structure was considered but dismissed as only utility data is available split by PFS response and PFS stable disease (there is currently no resource use data available split by response/non-response) and the use of this approach would add significant complexity to the model.

It was decided that clinicians concerns with using a 3-state model could be addressed by maintaining a 3-state structure but with differential utility values derived for each treatment depending upon the response rate observed (see section 6.4.9 below).

This approach will capture the difference in response between the treatments whilst ensuring the model does not become overly complex.

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

This model structure is closely aligned with the clinical pathway identified in section 2.4 and is the approach typically used in the modelling of metastatic oncology with a simple extension to incorporate the impact of a response to treatment which clinicians felt was important for vemurafenib.

6.2.4 Please define what the health states in the model are meant to capture.

The 3-state design splits patients' survival into a relatively high quality of life pre-progression health state (PFS)) and a relatively low quality of life post-progression health state (Progressed Disease – PD).

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 some patients experience solely disease stabilisation (a lack of further disease progression) rather than a response. The progressed disease state is designed to simulate the relatively low quality of life period after first progression and prior to death.

The model structure is fully aligned with three of the primary objectives of treatment in metastatic melanoma; namely:

1. Inducing response and tumour burden reduction
2. Delaying disease progression
3. Prolonging life

This model structure and the health states utilised are typical of the approach used in the modelling of metastatic oncology and variants of this approach

have been utilised in numerous NICE STAs and MTAs previously (NICE TA227, NICE TA212, Fleeman et al 2010, Hoyle et al 2011).

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

See section 6.2.4. (above) for detail on the way in which the model's health states capture the main aspects of metastatic melanoma. In addition to these health states the costs and disutilities associated with adverse events were included in the model as detailed in section 6.4.9.

A synthesis of the reference arm of BRIM3 study, the control arm of the Robert 2011 study and data from the SEER registry (Xing 2010) was utilised to model underlying disease progression for patients treated with dacarbazine in the base-case. This approach is described in further detail in section 6.3.1. below.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 29: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	30 years	Sufficient to capture all meaningful differences in technologies compared and as per on-going ipilimumab metastatic melanoma appraisal	NICE Guide to Methods, Ongoing NICE STA of ipilimumab in second line metastatic melanoma.
Cycle length	One week	Sufficient resolution to capture all meaningful differences in technologies compared	NICE Guide to Methods
Half-cycle correction	Yes – Where appropriate	NICE reference case	NICE Guide to Methods
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case	NICE Guide to Methods
Discount of 3.5% for utilities and costs	Yes	NICE reference case	NICE Guide to Methods

Perspective (NHS/PSS)	Yes	NICE reference case	NICE Guide to Methods
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Yes. See Section 6.5.5. for further detail.

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

The model assumes patients receive treatment until disease progression.

Whilst there is precedent in considering the role of early discontinuations in NICE appraisal of other TKIs (for example erlotinib in the ongoing STA in EGFR M+ mNSCLC) in the case of vemurafenib early discontinuation appears to have occurred extremely rarely (with down-dosing favoured) and so in the model it is assumed that patients receive treatment until disease progression.

6.3 Clinical parameters and variables

6.3.1 Please demonstrate how the clinical data were implemented into the model.

6.3.1.1. Model Overview

The model created is a partitioned survival model which treats PFS and OS as individual entities (i.e. no assumption is made about the relationship between the two) and then derives the proportion of patients in the PD health state as the difference between the two curves (as a patient who is alive but is no longer in PFS must be in the progressed disease state). The proportion of patients in each of the two PFS health states is then derived using the response rates observed for both dacarbazine and vemurafenib.

6.3.1.1 Data Used to model PFS and OS

The model was developed utilising the March 2011 cut of the BRIM3 data. This cut of data featured the all variables required to build an economic model (PFS, OS, Response Rates, Dosing etc).

This data is a more mature version of that published in the NEJM (with around 4 months further follow-up).

Whilst a further cut of BRIM3 was taken in October 2011 only Overall Survival data is available from this cut-off (i.e. no Progression Free Survival, Response Rate or dosing data is available) and so it is not possible to build an economic model using *solely* this cut of the data.

The October 2011 cut was taken in order to achieve EMA regulatory approval in as short a timeline possible following initial questions surrounding the maturity of the BRIM3 data and so solely OS data was cleaned and no other data is available.

By this point in time cross-over had increased to 24% (compared to only 7% in the March cut). Due to this crossover it may be argued that whilst the October cut is more mature than the March cut it is also more confounded by crossover and so less representative of the outcomes expected in UK clinical practice if vemurafenib were to be approved by NICE. This hypothesis appears to be supported by a comparison of the two cuts (discussed further in

Section 6.3.1.3) and indicates that the March data is likely to be most representative for the current decision problem.

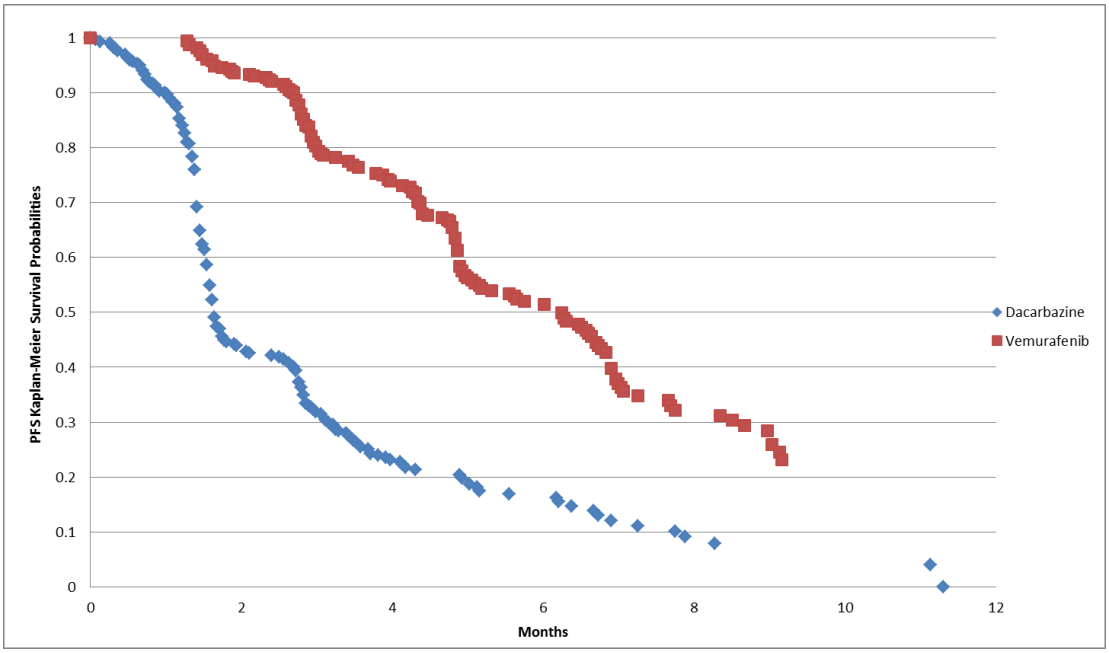
The October 2011 OS data combined with the March 2011 dosing, PFS and response rate data was used in sensitivity analysis.

The derivation of the base-case PFS and OS curves based upon the March cut is explained below.

6.3.1.3 Progression Free-Survival

The PFS curves from the March 2011 cut of BRIM3 are presented in Figure 26 below.

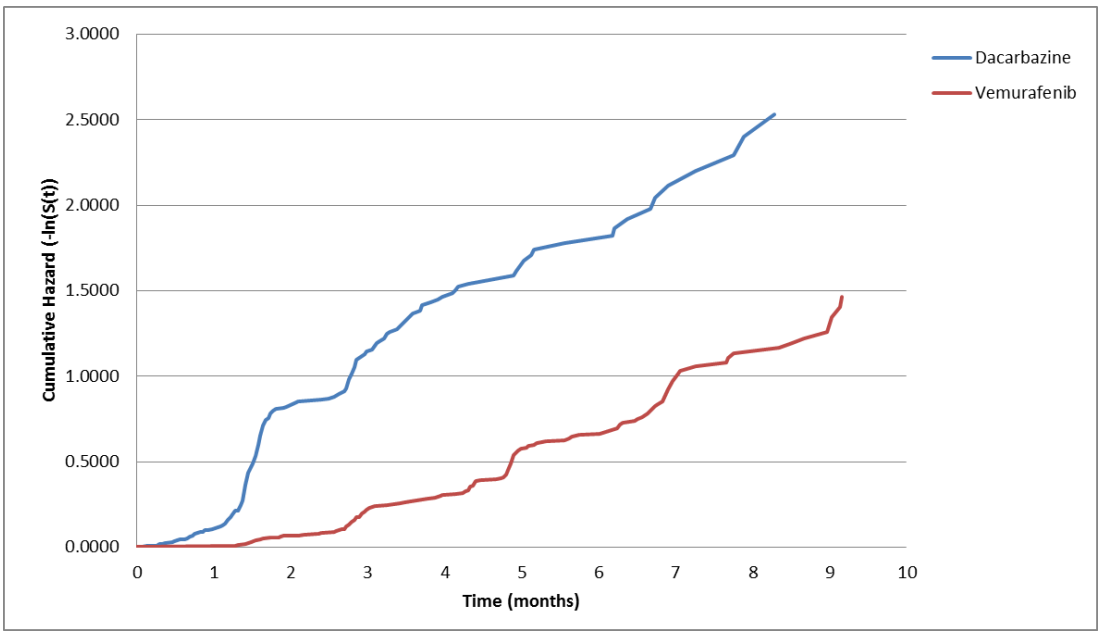
Figure 26: BRIM3 PFS Curves (March 2011 cut-off)



These curves demonstrate the extremely poor outcomes experienced by BRAF V600 mutation positive metastatic melanoma patients if treated with dacarbazine alone and the substantial impact the use of vemurafenib could have for these patients (with median PFS almost quadrupled via introduction of vemurafenib (6.2 months vs 1.6 months)).

Figure 27 below demonstrates the cumulative hazard plot derived utilising the above Kaplan-Meier data (a simple negative log transformation).

Figure 27: BRIM3 PFS Cumulative Hazard Plots



Interpreting Cumulative Hazard Plots

Whilst survival data is typically presented in the form of KM plots, the production of cumulative hazard plots allows simple examination of the trends in the data that can be difficult to interpret using KM data alone.

The slope of the cumulative hazard plot at any point in time can be interpreted as the hazard of the event of interest occurring at that point in time. The steeper a cumulative hazard plot is the higher the hazard of the event occurring and the flatter a cumulative hazard plot is the lower the hazard of the event occurring is.

This property allows consideration of how the risk of an event occurring changes over time (i.e. *how does the slope change over time?)* and the way in which the impact of some intervention changes over time (i.e. *how much does the ratio of the two slopes (the hazard ratio) change over time?).* This analysis is potentially important when considering extrapolating data as it can inform

both the extrapolation of the baseline risk without the intervention (i.e. *if the slope (hazard) of the cumulative hazard plot for the non-intervention curve has been straight for the period observed it may be reasonable to continue with a straight hazard beyond this point in time*) and how the intervention arm may differ from that baseline risk if further follow-up were available (i.e*. if the ratio of the two slopes (hazard ratio) has been constant throughout the data it may be reasonable to continue that ratio beyond the period of follow-up).* Failure to consider changes in either baseline risk or hazard ratio over time when extrapolating can result in survival curves erroneously based upon 'averages' rather than stabilised hazard/hazard ratio trends with resultant poor face validity.

Figure 27 above demonstrates clearly that vemurafenib is associated with a lower average hazard of a PFS event (progression or death) occurring than if treated with dacarbazine alone (i.e. on average the slope of the red line is lower than the blue one).

The effect of vemurafenib is perhaps most noticeable in the first two months of the study in which the PFS hazard in the dacarbazine arm is substantially higher than in the vemurafenib arm (the dacarbazine arm cumulative hazard is very steep relative to the vemurafenib plot which barely deviates from the x-axis in this period). If this period is considered alone with individual exponential hazards estimated for each arm the hazard of experiencing a PFS event in the dacarbazine arm is over 12 times higher than for a patient given vemurafenib (with an associated PFS HR of around 0.08 attributed to the use of vemurafenib in this period).

If the period from month 2-4 is considered in a similar manner the hazard of experiencing a PFS event in the dacarbazine arm remains over 2.5 times higher than in the vemurafenib arm (with a PFS HR of around 0.38).

These hazard trends clearly demonstrate the rapid efficacy of vemurafenib and its ability to slow an extremely aggressive disease with a median PFS of

around 6 weeks if treated with dacarbazine, to a rate at which no PFS events had occurred in the first 6 weeks of vemurafenib treatment (BRIM3 March 2011 cut-off). At an advisory board held in support of the development of the economic model clinicians were keen to emphasise their experience of the ability of vemurafenib to demonstrate a rapid effect on their patients' disease and this anecdotal evidence does appear to be borne out by examination of the BRIM3 PFS cumulative hazard plots.

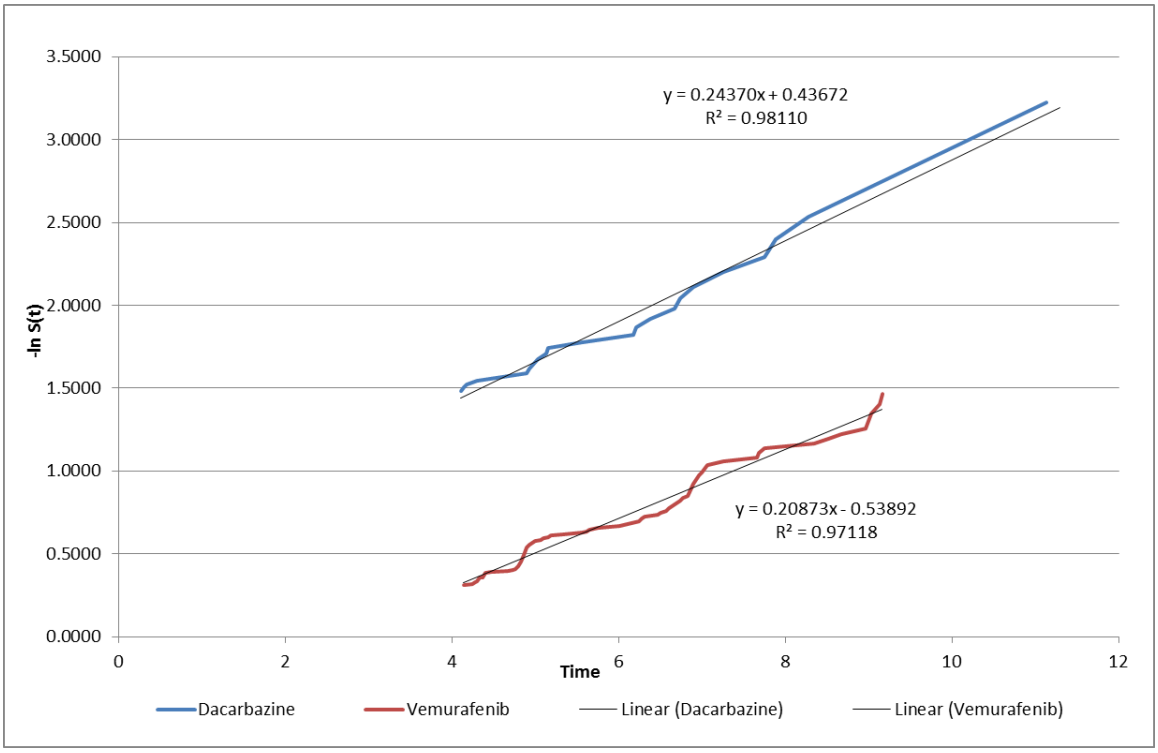
From around month 4 onwards the hazard of experiencing a PFS event in the vemurafenib arm appears to increase relative to that observed in the first 4 months (the curve appears to steepen) whilst in the dacarbazine arm the hazard of experiencing an event appears to decrease. In both arms the curves then appear to stabilise from this point in time (i.e. they are straight).

If month 4 onwards is considered as its own defined period it is clear that the absolute hazard of experiencing an event if given vemurafenib remains lower than if given dacarbazine but that the ratio of the two slopes is now closer from this point onwards than in the first 4 months (i.e. the hazard ratio is still lower than 1 but not as low as it was in the previous period).

The PFS HR from this point onwards (assuming an exponential function for each arm) is around 0.86 (0.20873/0.24370 = 0.86) (see

Figure 28 below).

Figure 28: BRIM3 PFS Cumulative Hazard Plot (Month 4 onwards)



The observation that the hazard ratio is somewhat eroded from this point in time is potentially important when extrapolating the BRIM3 data as the cumulative hazard plot appears to suggest that it would be inappropriate to attempt to claim that the hazard ratio simulated beyond follow-up should be informed by an 'average HR' (i.e. the HRs normally estimated from clinical

trials under the assumption of proportion hazards) as the treatment effect observed in this first four months is not representative of that seen from month 4 onwards.

This observation may also give some indication as to why the reported PFS HRs associated with vemurafenib (in effect average HRs under the assumption of proportion hazards) increased between the first and second data cuts. As more and more data is collected the this initial extremely low hazard ratio first four month period is likely being ‘watered down’ by the later follow up which includes more of the period after 4 months in which the hazard ratio (whilst still less than 1) is higher than the initial period (causing the average hazard ratio to be pulled upwards).

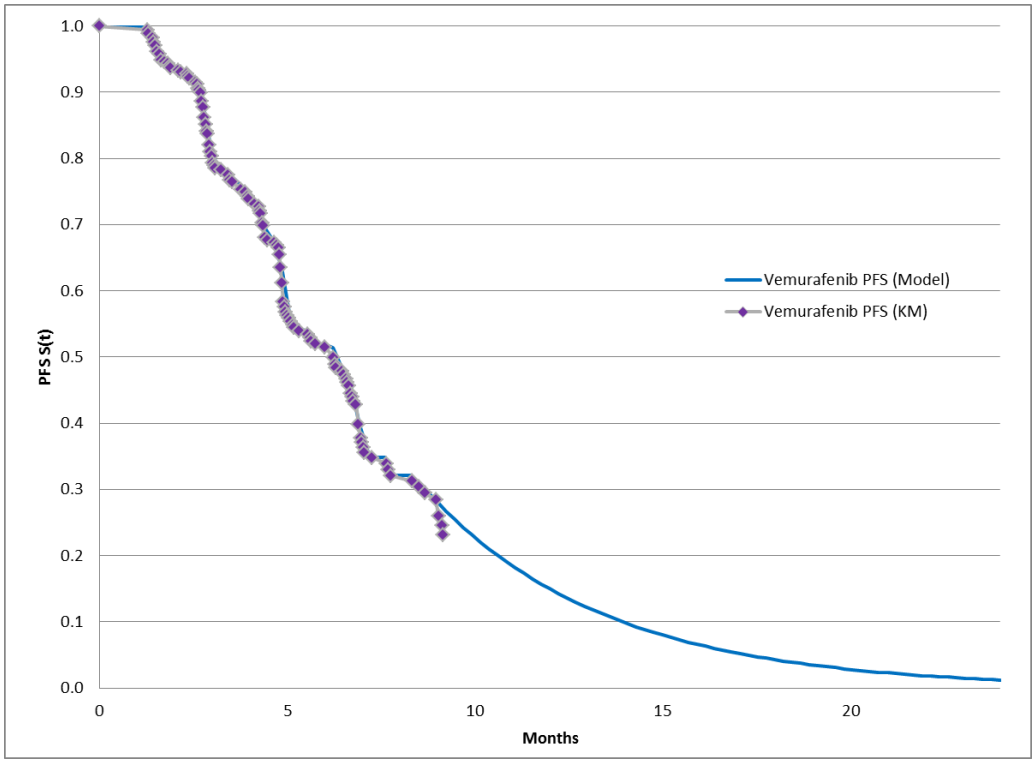
Following the observation that the vemurafenib arm hazard was relatively stable from month 4 onwards it was hypothesised that the data supported the use of an exponential function derived using data from month 4 onwards only when extrapolating this curve (i.e. using the hazard shown in

Figure 28 above).

After inspection of the cumulative hazard plot it was hypothesised that a transition point of month 9 (week 39) should be used between the KM curve and the parametric tail as this appeared to be one of the last point of convergence between the observed cumulative hazard trend and that

predicted via the exponential model fitted. Figure 29 below demonstrates the excellent face validity of the modelled vemurafenib PFS curve using this hazard and transition point.

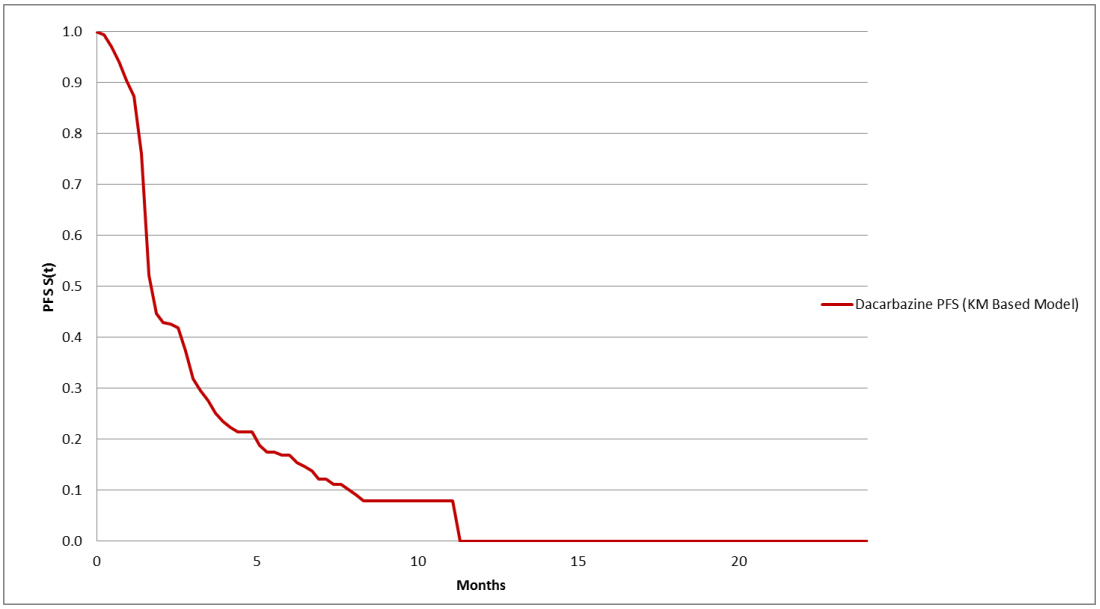
Figure 29: Vemurafenib PFS Extrapolation



Whilst the dacarbazine arm was technically complete it was felt that the 'step and drop' observed in its tail was likely an artefact of the small patient numbers involved at this point of the curve (see Figure 30 below) and so an exponential tail based upon data from month 4 onwards was fitted on to the KM data (as was done for vemurafenib and as presented in

Figure 28) in order to ‘smooth’ the step out.

Figure 30: Dacarbazine PFS curve ‘step’ in tail



Month 7 was chosen as the transition point between the observed KM and the exponential tail as this appeared one of the last points on the KM at which point the data remained reliable (i.e. the curve was yet to become erratic).

Figure 31: Vemurafenib PFS curve ‘step’ in tail

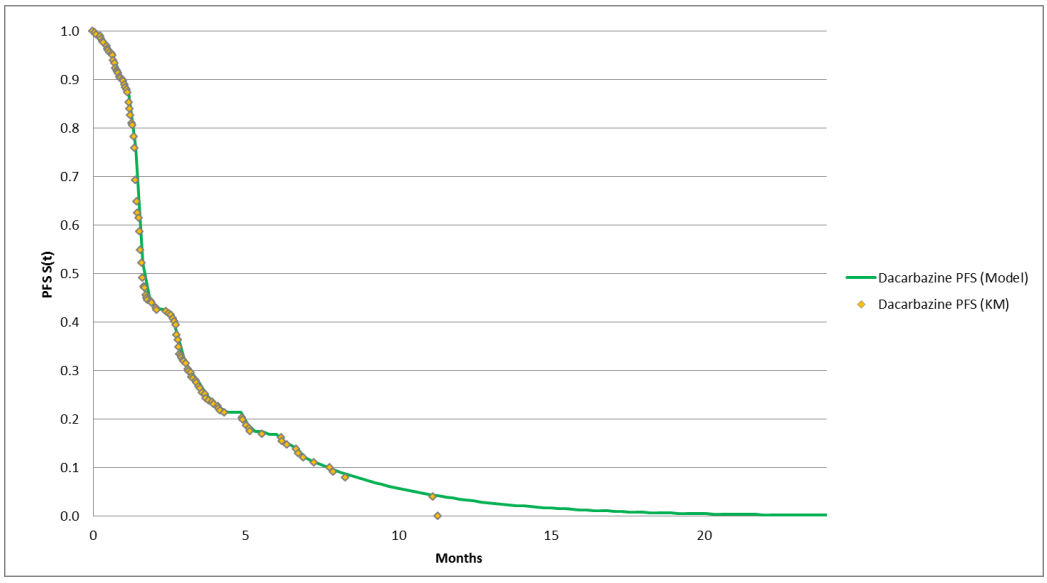
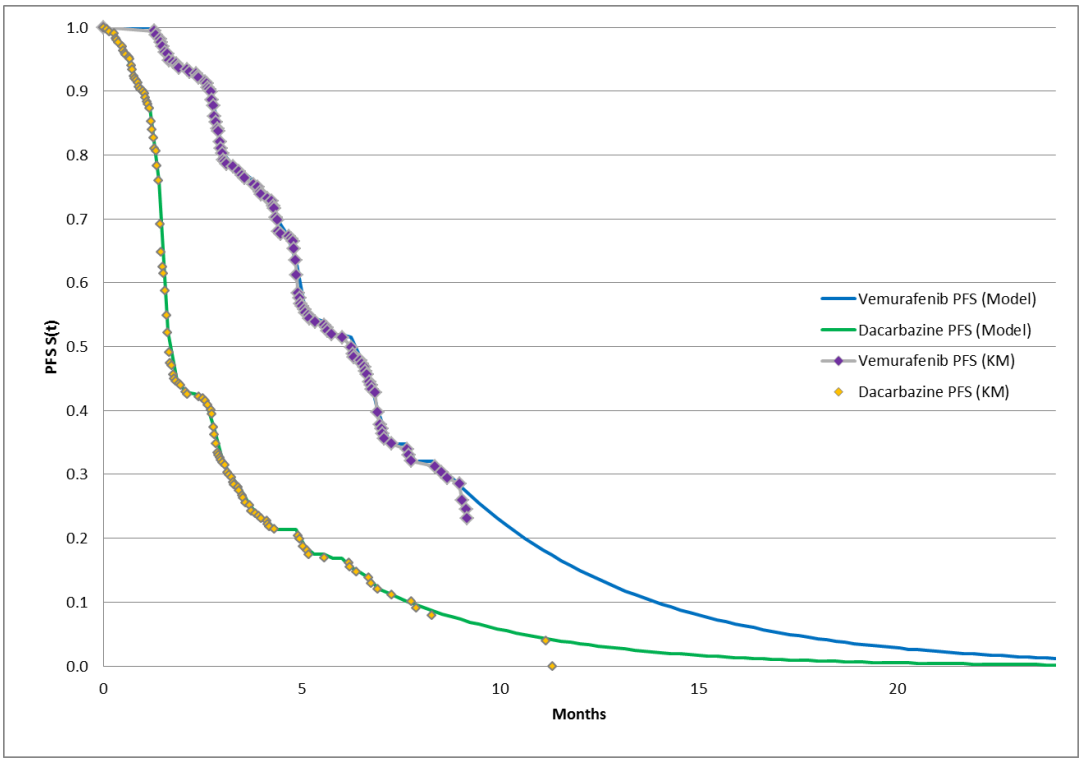


Figure 31 above demonstrates the excellent face validity of this extrapolation compared to the KM data observed and Figure 32 below presents the PFS curves fitted for each arm.

Figure 32: Modelled PFS curves



As detailed for overall survival below it is questionable whether the use of a simple single exponential function is appropriate when extrapolating time to event data in melanoma (as the risk of an event occurring appears to decline over time (despite BRIM3 not yet showing that trend)).

Whilst a simple exponential function has been employed for extrapolating both PFS curve in the base-case the use of alternative declining hazard curves may also be appropriate in this population (see Section 6.3.1.3).

Given the magnitude of the ICERs estimated in the base-case and the fact that increasing the time patients given vemurafenib spend in PFS will increase the ICER (as vemurafenib is given to progression and the cost of one month's treatment is higher than NICE's valuation of one month of life) the use of these declining hazard curves has not been explored.

6.3.1.3 Overall survival

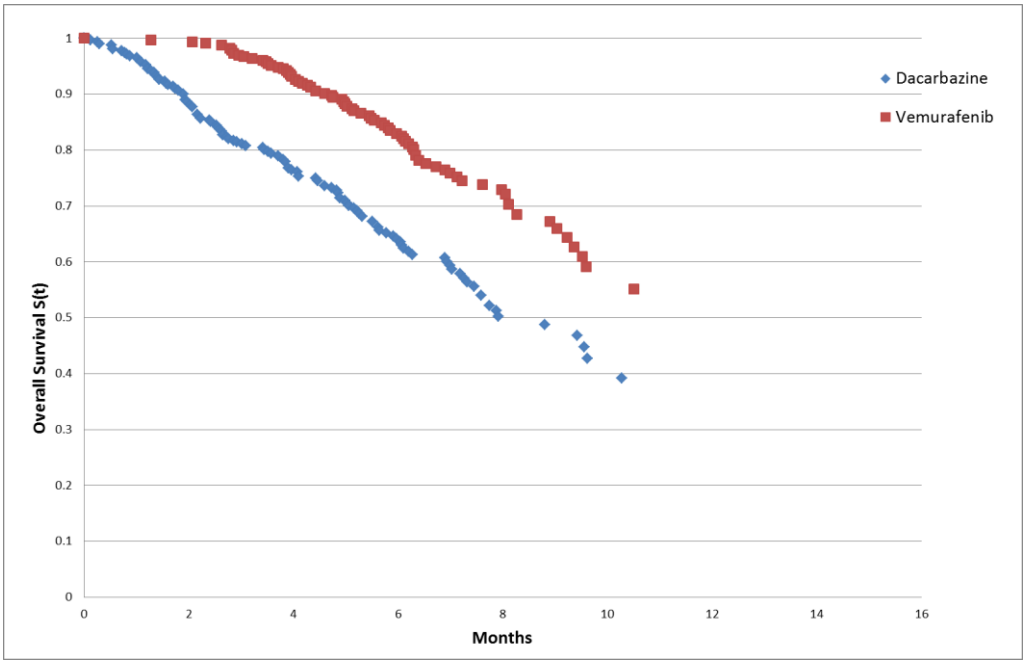
In the base- case modelling a synthesis of the March 2011 BRIM3 data-cut, the reference arm of the Robert 2011 RCT and data from the SEER registry

(Xing 2010) was utilised to model overall survival for both vemurafenib and dacarbazine. This modelling is detailed below.

The use of the March rather than October OS data

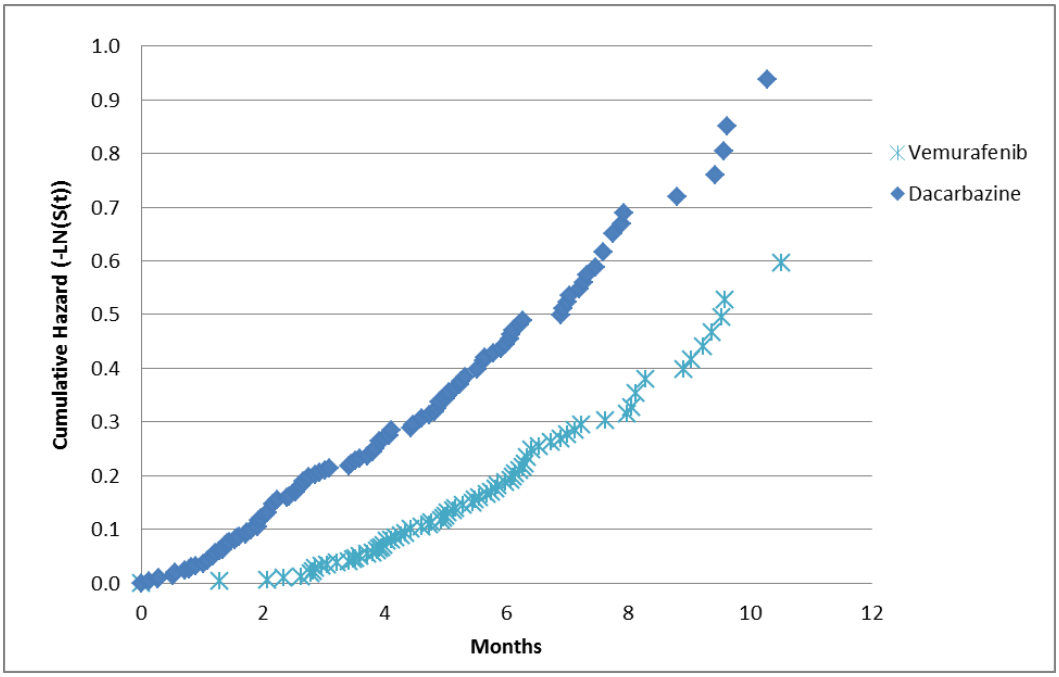
The figure below shows the OS KM curves from the March 2011 data-cut of the BRIM3 RCT.

Figure 33: BRIM3 March 2011 OS KM curves



The cumulative hazard plot associated with the above KM data is provided below.

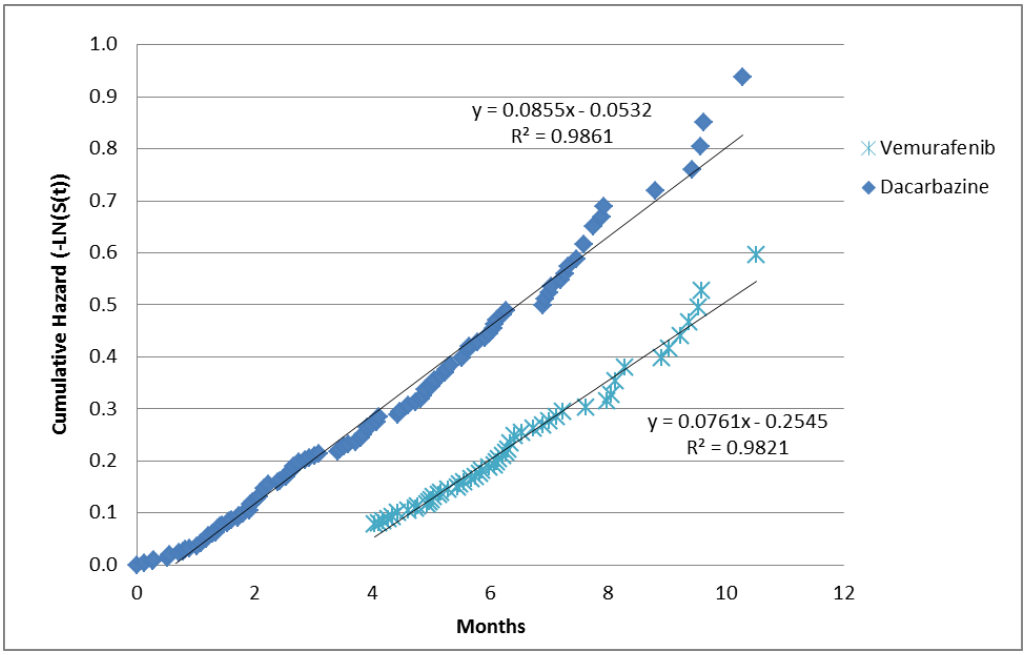
Figure 34: BRIM3 March 2011 OS Cumulative Hazard Plots



The cumulative hazard plot above indicates that for the period observed (around 10 months) the dacarbazine hazard of death appears fairly constant (r^2 for linear fit = 0.9861) whilst the vemurafenib arm features an extremely low hazard initial period (for approximately 4 months) followed by a higher hazard period with a hazard closer to that experienced by patients receiving dacarbazine (albeit slightly lower for vemurafenib (OS HR from month 4 onwards is approximately 0.89 (the ratio of the two hazard estimated in Figure **35** below)). The OS cumulative hazard trend observed in the vemurafenib arm appears very similar to that seen for PFS in BRIM3 (with a very low hazard period in the first 4 months followed by a rise and then 'stabilisation' at a hazard closer to that for dacarbazine).

As was the case for PFS the combination of this initial extremely low hazard ratio period and higher hazard ratio period from month 4 onwards (although still below 1) suggests that as more and more follow-up of the BRIM3 RCT becomes available so the OS HR observed will increase (as has been seen in the 3 cuts taken to date).

Figure 35: BRIM3 March 2011 OS Cumulative Hazard Plots



In addition to the March 2011 cut there is also overall survival data available from an October 2011 data-cut.

Figure 36: BRIM3 October 2011 OS KM curves

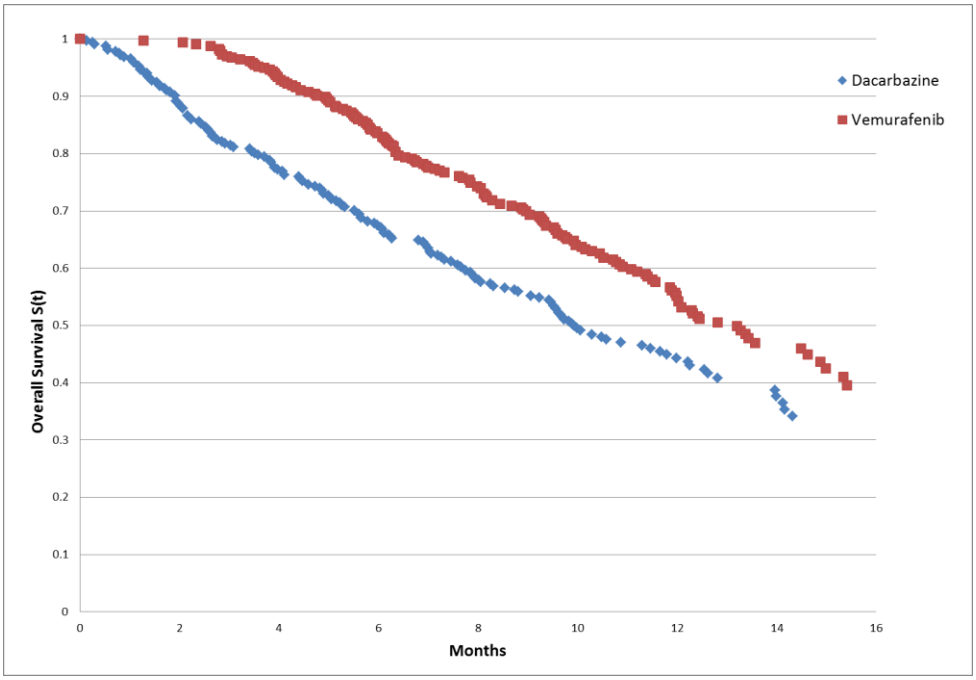
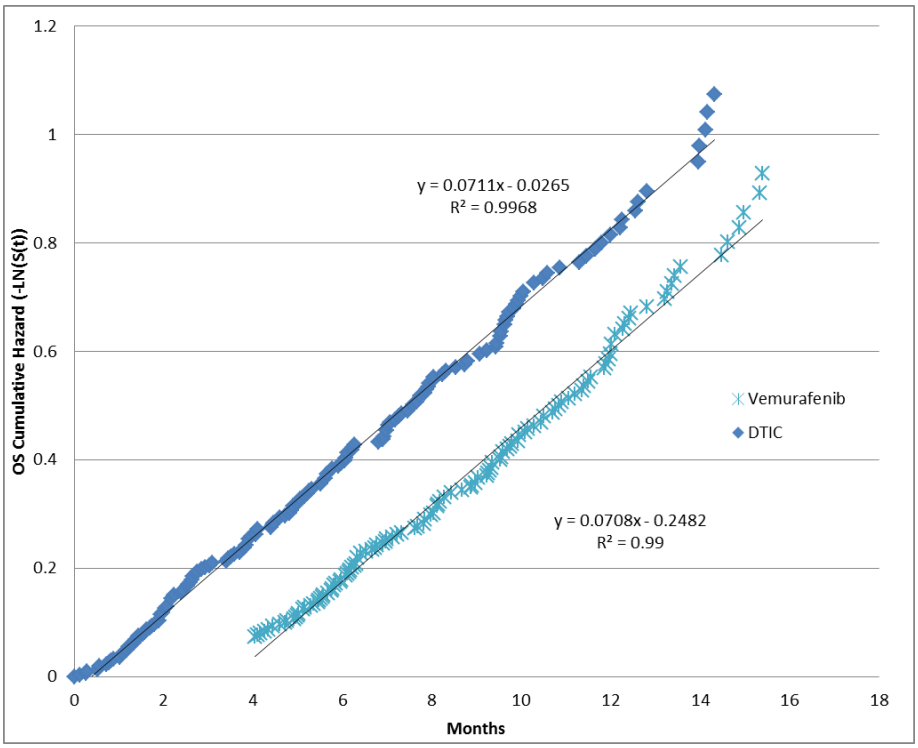


Figure **35** figure above shows the OS KM from this cut of the data whilst

Figure 37 below is the cumulative hazard plot for the same data.

Figure 37: BRIM3 October 2011 OS Cumulative Hazard Plots



In this cumulative hazard plot very similar trends as were observed in the earlier cut are seen (notably a stable hazard in the dacarbazine arm throughout the curve and a very low hazard for the first four months of the vemurafenib arm followed by a constant higher hazard period until the end of follow-up).

However if the two data-cuts are compared quantitatively then it is clear that whilst the overall trends are similar something appears to have changed between the two cuts which has influenced the hazard of death in the dacarbazine arm more than that in the vemurafenib arm (thereby skewing the hazard ratio observed from month 4 onwards).

If the October 2011 cut is compared with the March 2011 cut the monthly hazard of experiencing an event in the vemurafenib arm from month 4 onwards drops by around 7% (from 0.0761 to 0.0708) whilst the dacarbazine arm monthly hazard drops by 17% (from 0.0855 to 0.0711).

This drop in the absolute hazard associated with dacarbazine means that from month 4 onwards rather than continuing to diverge (as they did in the March 2011 cut shown in
Figure **35** above) the cumulative hazard plots based upon the October 2011 cut run virtually parallel (indicating a HR approaching 1 from this point onwards).

When assessing this later cut it is important to note that following the positive interim analysis of BRIM3 conducted in December 2010 the study was ended and cross-over permitted. The consequence of this is that by October 2011 24% of patients had crossed over to receive vemurafenib (compared to only 7% in March 2011). It may therefore be hypothesised that the dacarbazine hazard from this later cut is positively confounded by the use of vemurafenib in those patient who crossed over.

This hypothesis appears to be supported by Figure 38 and

Figure **39** in which the two cuts of the data are compared to data from another RCT in which dacarbazine was utilised as a reference arm (Robert 2011 – ipilimumab + dacarbazine vs dacarbazine in patients previously untreated advanced melanoma patients).

Figure 38: BRIM3/Robert dacarbazine OS KM curves (March cut)

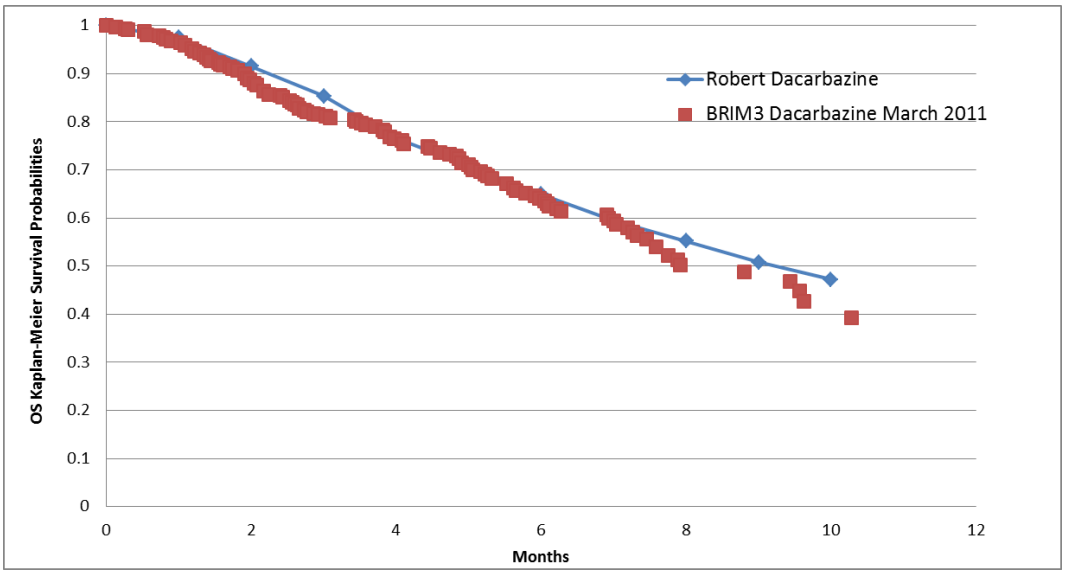
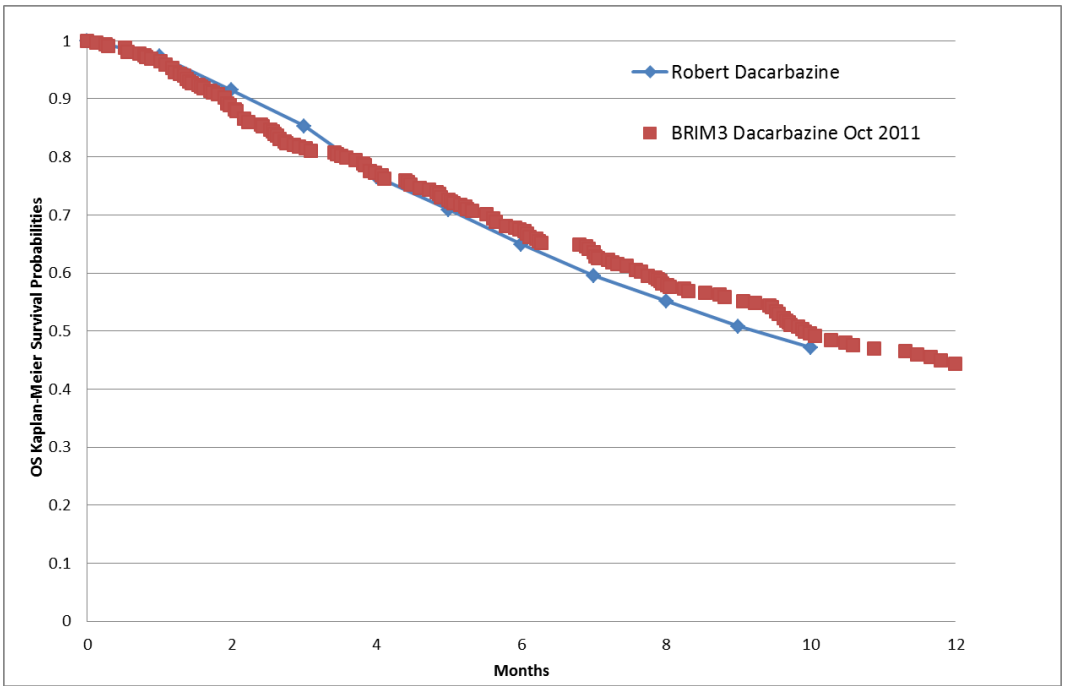


Figure 39: BRIM3/Robert dacarbazine OS KM curves (October cut)



In the above two diagrams it appears clear that whatever has happened to the dacarbazine arm between the two cuts appears to have happened after month 4. Prior to this point in time the two BRIM3 cuts appear to be equivalent and

seem to ‘trace’ the Robert data fairly well. However if you consider month 4 onwards only in each figure it is clear that whilst the March cut dacarbazine arm continues along the trend of the Robert curve the October cut is now ‘flatter’. This is highly suggestive of the influence of crossover as those patients who did crossover from dacarbazine to vemurafenib will have received and progressed on first line dacarbazine prior to crossing over.

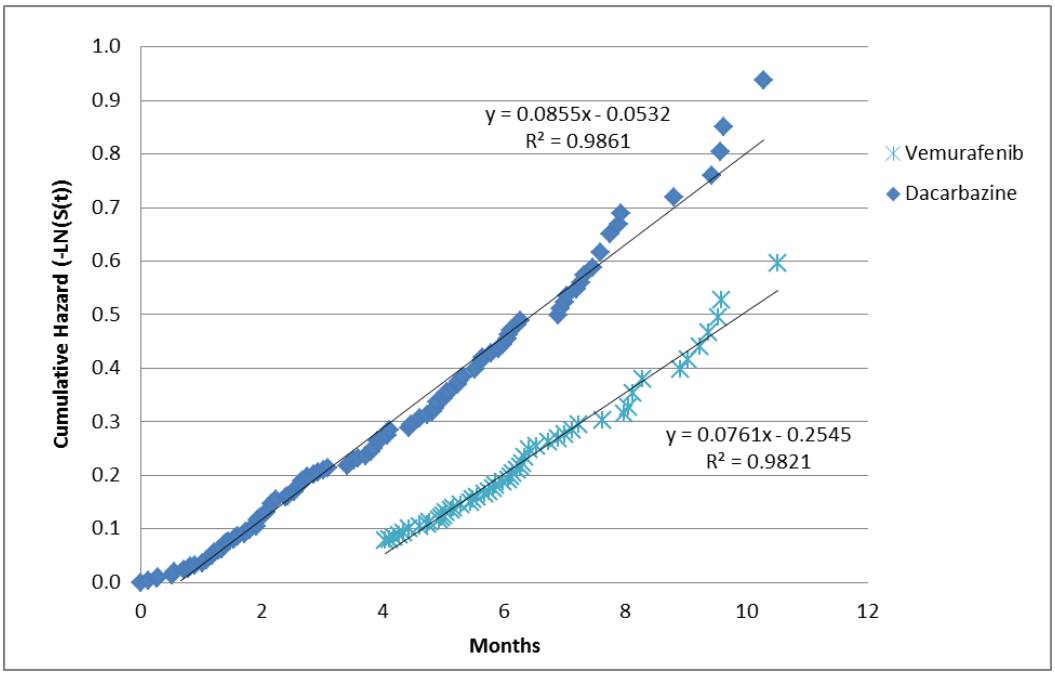
When the extremely low hazard initial period in the vemurafenib arm of BRIM3 is considered in light of the 17% drop in absolute hazard observed between the two cuts it appears clear that crossover has had a confounding influence upon the October 2011 cut dacarbazine arm. In light of this confounding, the March cut is assumed to be more representative of the outcomes expected of patients treated with dacarbazine in England/Wales than the October cut and so has been used in the base-case modelling.

Whilst there are now a range of novel techniques that may be utilised to adjust for cross-over (RPSFT models, the Branson and Whitehead approach, IPCW etc (Morden 2010)) it is not possible to utilise these methods given the data from the October BRIM3 data as they are reliant upon the ability to access more data than simply the OS time to event values.

Extrapolation suggested March 2011 OS data

As noted above in the March cut of BRIM3 the dacarbazine arm features a constant linear monthly hazard (of around 0.0855, r^2=0.9861) whilst the vemurafenib arm featured an initial low hazard period of around 4 months followed by a constant hazard period (0.0761 monthly hazard, r^2=0.9821). This equates to a hazard ratio of around 0.89 (0.761/0.855) from month 4 onwards (see Figure 40 below for the derivation of these figures).

Figure 40: BRIM3 March 2011 OS Cumulative Hazard Plot

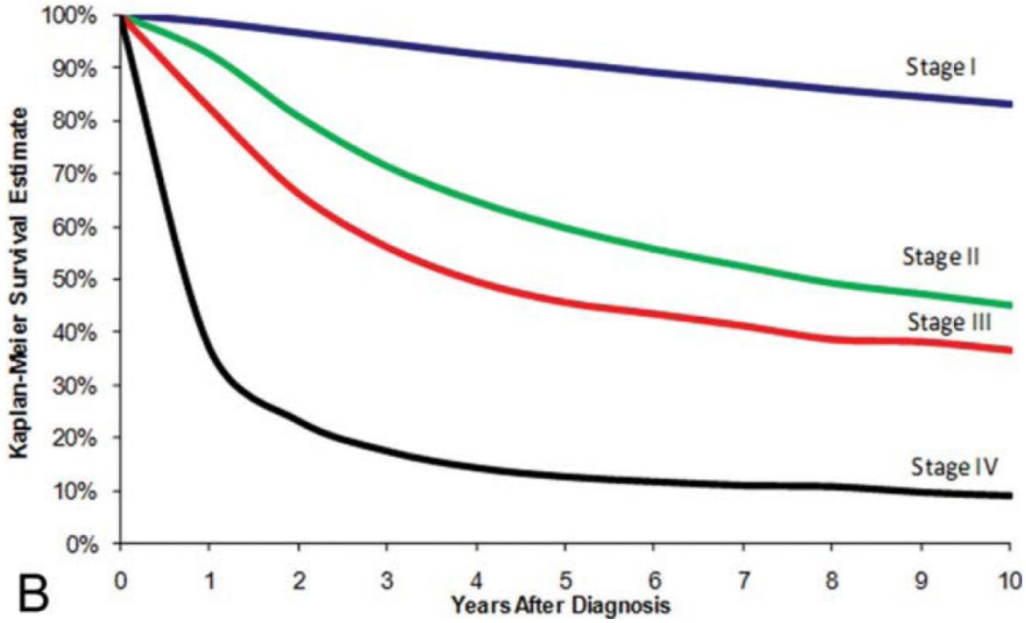


If considered in isolation these plots appear to suggest that it would be appropriate to extrapolate the OS data from BRIM3 using the two 'stabilised hazards' presented in the figure above until the x-axis is reached (via individual exponential functions for each arm). However, whilst this approach has been utilised in previous NICE appraisals of oncology technologies in other disease areas (erlotinib for the first line treatment of EGFR-TK mutation positive mNSCLC (ongoing)), in the case of advanced melanoma the assumption that the risk of death is time invariant appears inappropriate.

Modelling baseline risk

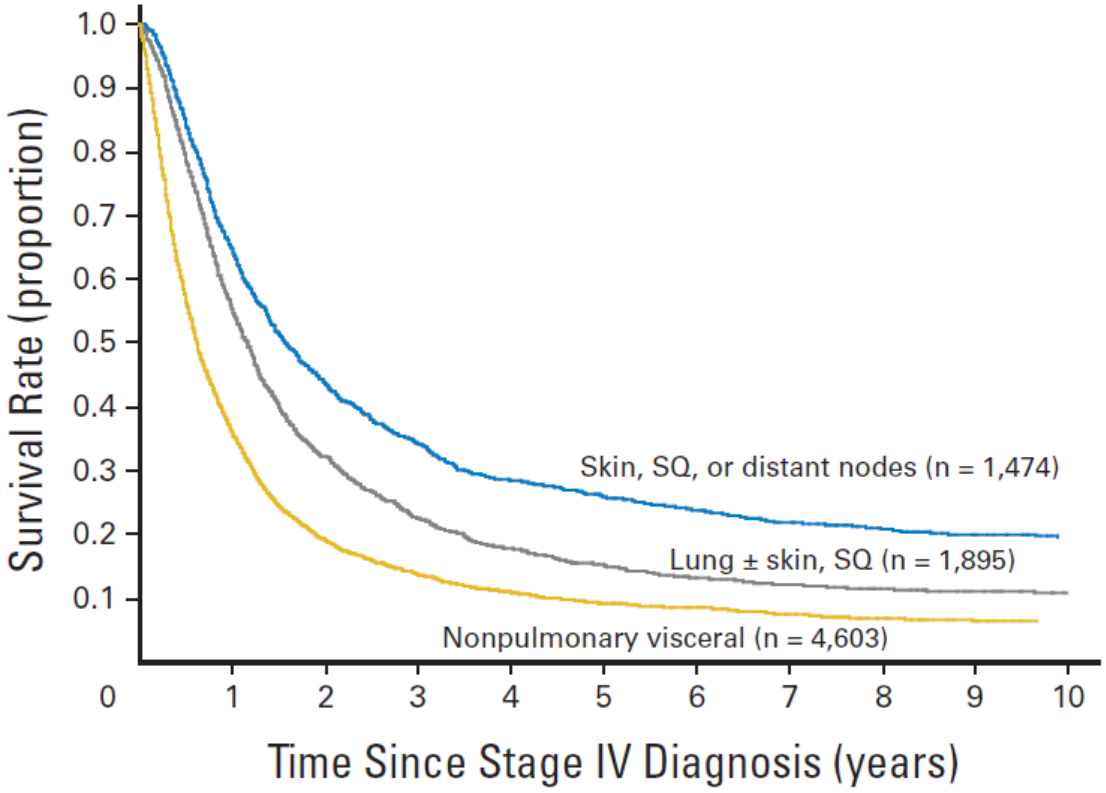
Data from the US 'SEER' (Surveillance Epidemiology and End Results) registry indicates that whilst around 60% of those patients diagnosed with stage IV melanoma will have died within 1 year of diagnosis around 15% of patients will be alive 4 years after diagnosis and **9.1%** of patients will still be alive 10 years after diagnosis (see Figure 41 below (Xing et al 2010 - analysis includes over 1,000 stage IV patients).

Figure 41: SEER registry OS curves (Xing 2010)



This trend is from the SEER registry is supported by the below data from Balch 2009 which features nearly 8,000 patients diagnosed with stage 4 disease. This data suggests that there is a strong correlation between site of metastasis and expected survival (with over 20% of patients with Skin, SQ or distant node metastasis alive at 10 years compare to an (estimated as this data point has not yet been reached in the below figure) 8% of patients with non-pulmonary visceral metastasis).

Figure 42: Balch 2009 OS curves



This real-world data suggests that metastatic melanoma is disease with significant heterogeneity in expected overall survival depending upon patient characteristics (Balch 2009) and a disease in which the risk of death in a given year appears highly conditional upon the time after initial diagnosis (Xing 2010).

In addition this real world data a number of clinical trials with longer follow up than the BRIM3 RCT demonstrate that the risk of death declines over time. Figure 43 and Figure 44 are two studies in which dacarbazine was utilised as a reference arm (the Robert study mentioned previously and the Bedikian study in which dacarbazine was compared to dacarbazine + DHA-paclitaxel).

Figure 43: Robert 2011 OS curves

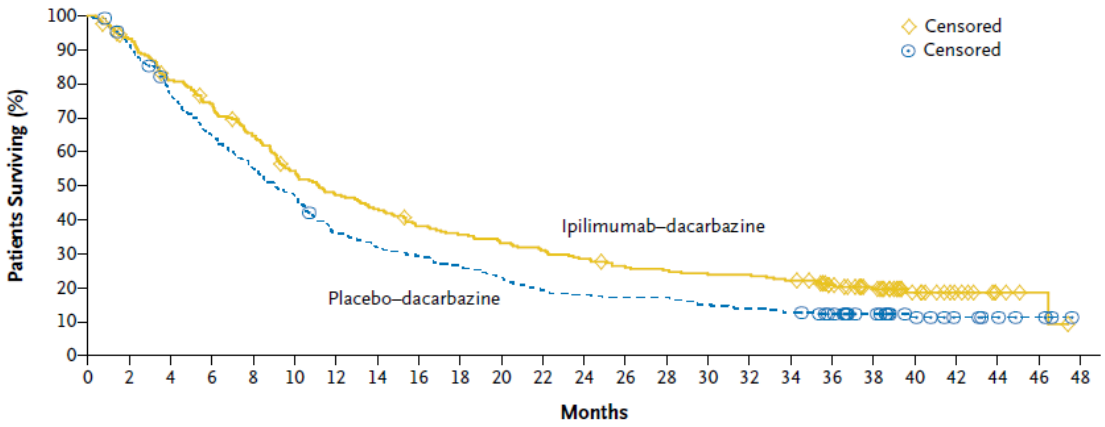
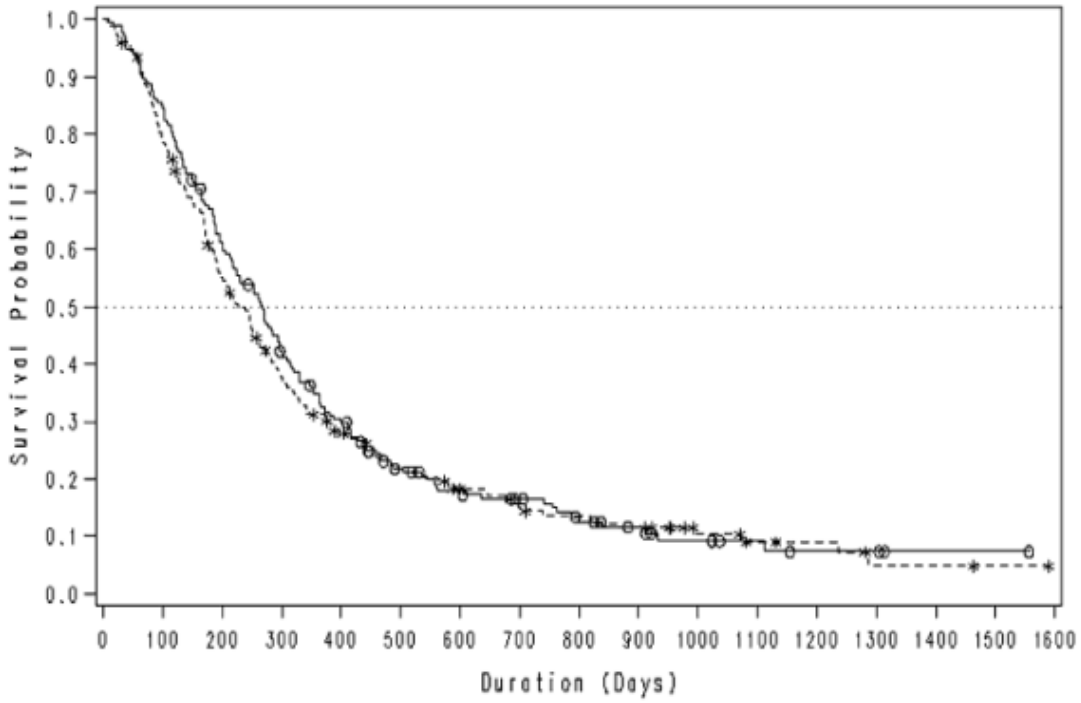


Figure 44: Bedikian 2011 OS Curves



Note: The dotted line above is DHA-paclitaxel + dacarbazine (demonstrated to not be efficacious) whilst the un-dotted line is dacarbazine monotherapy.

It is important to consider this reducing hazard over time when building an economic model in melanoma as failure to do so will result in survival curves that reach the x-axis prematurely and have poor face validity when compared to historical data. It is clear from each of the figures above that if someone was given access to only the first 12 months data from each study (the time period for which data from BRIM3 is available) and had not seen any other

data in melanoma they would produce curves that would be completely unrepresentative of the curves actually observed (as the relatively high risk of death observed in the first 12 months of each data source would simple be continued).

It is unclear as to whether this declining hazard trend would be expected to occur in *specifically* BRAF V600 mutation positive patients as the role of BRAF mutations in melanoma is a relatively recent discovery and data relevant to this question does not yet exist. However in order to model the decision problem an assumption of the baseline risk of these patients must be made.

Comparing the BRIM3 and the Robert control arms

Following consultation with clinical experts it was suggested that the data available from the control arm of the Robert 2011 study (in which ipilimumab + dacarbazine was compared to dacarbazine alone in previously untreated advanced melanoma patients (BRAF mutation status unknown)) may provide a useful reference point with which to extrapolate the BRIM3 control arm.

As shown in Figure 45 and Figure 46 below the control arms of the two studies appear almost indistinguishable for the period data from BRIM3 is available.

Figure 45: BRIM3/Robert dacarbazine OS KM curves (March cut)

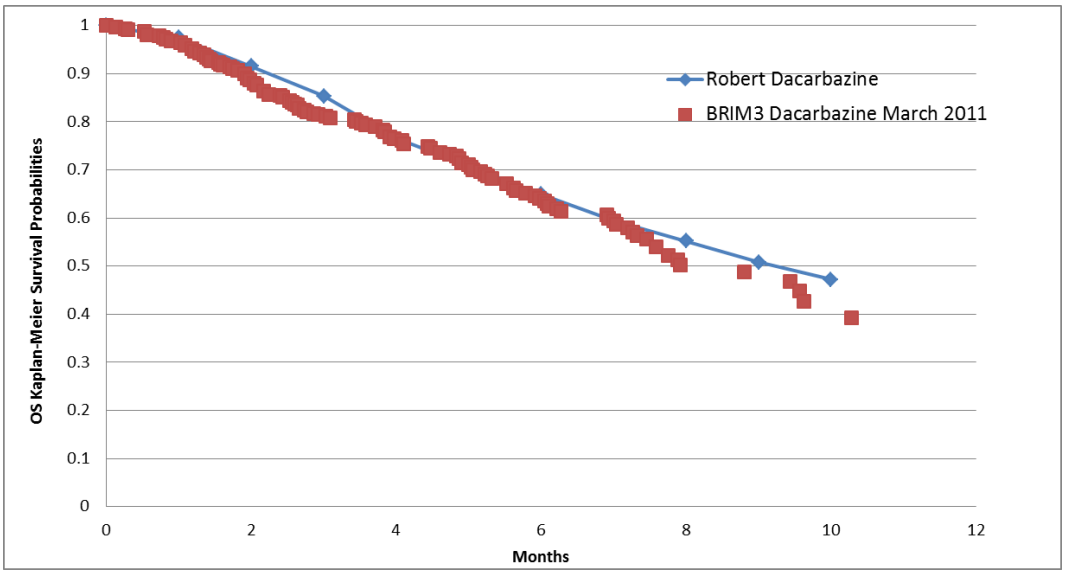
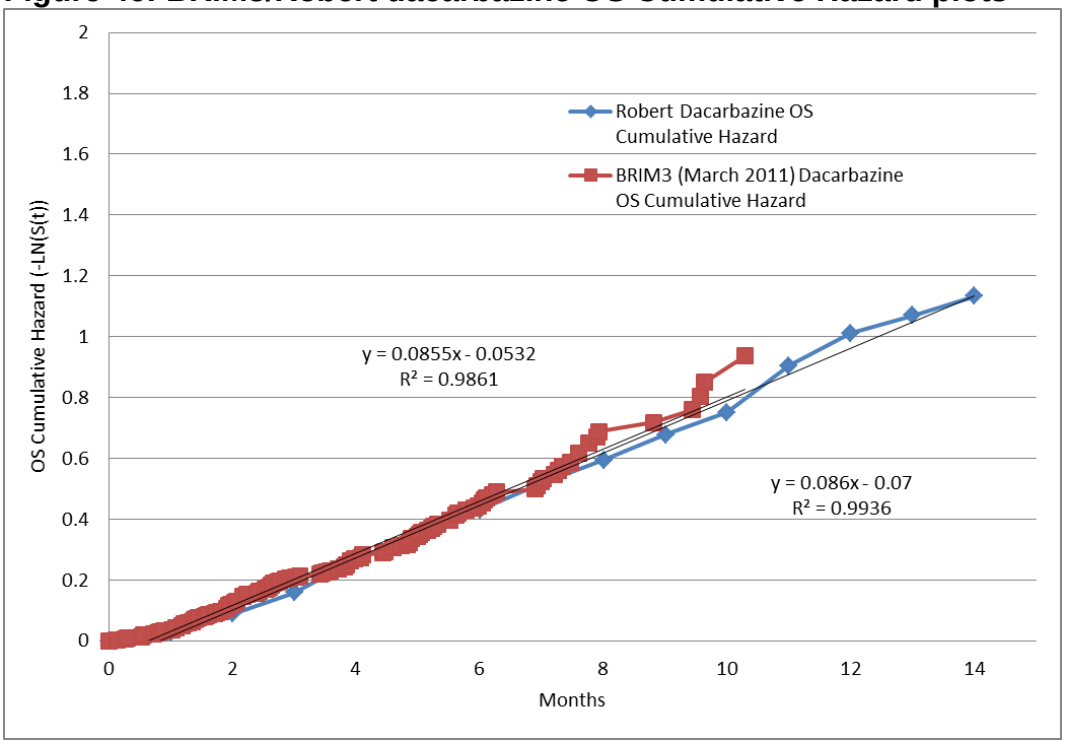


Figure 46: BRIM3/Robert dacarbazine OS Cumulative Hazard plots



Note: First 14 months of Robert used in above figure for the reasons detailed below figure 46.

The patient characteristics from the two studies are summarised below:

Table 30: Patient Characteristics (Robert 2011 left, BRIM3 right)

Table 1. Demographic and Baseline Clinical Characteristics of the Patients.*

Characteristic	Ipilimumab plus Dacarbazine (N=250)	Placebo plus Dacarbazine (N=252)
Mean age — yr	57.5	56.4
Sex — no. (%)		
Male	152 (60.8)	149 (59.1)
Female	98 (39.2)	103 (40.9)
ECOG performance status — no. (%)†		
0	177 (70.8)	179 (71.0)
1	73 (29.2)	73 (29.0)
Metastasis stage — no. (%)‡		
M0	6 (2.4)	8 (3.2)
M1a	37 (14.8)	43 (17.1)
M1b	64 (25.6)	62 (24.6)
M1c	143 (57.2)	139 (55.2)
Lactate dehydrogenase — no. (%)		
≤ULN	157 (62.8)	140 (55.6)
>ULN	93 (37.2)	110 (43.7)
Unknown	0	2 (0.8)
Prior adjuvant therapy — no. (%)	66 (26.4)	67 (26.6)

Table 1. Baseline Demographic and Clinical Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Vemurafenib (N=337)	Dacarbazine (N=338)
Median age (range) — yr	56 (21–86)	52 (17–86)
Male sex — no. (%)	200 (59)	181 (54)
White race — no. (%)†	333 (99)	338 (100)
Geographic region — no. (%)		
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 performance status — no. (%)‡		
0	229 (68)	230 (68)
1	108 (32)	108 (32)
Extent of metastatic melanoma — no. (%)§		
M1c	221 (66)	220 (65)
M1b	62 (18)	65 (19)
M1a	34 (10)	40 (12)
Unresectable IIIC	20 (6)	13 (4)
Lactate dehydrogenase — no. (%)¶		
≤Upper limit of the normal range	142 (42)	142 (42)
>Upper limit of the normal range	195 (58)	196 (58)

These patient characteristics appear reasonably well balanced and suggest the two studies are broadly comparable (as indicated by the KM and cumulative hazard comparisons presented previously). The only clear difference between the two studies is that BRIM3 was conducted in exclusively BRAF V600 mutated patients whilst Robert was conducted in patients with unknown BRAF mutation status.

During consultation with clinical experts it was suggested that as the BRIM3 and Robert dacarbazine arms appeared so similar for the first 12 months of follow-up it might be reasonable to assume that this would be the case for the remainder of the Robert data (i.e. it may be appropriate to model the BRIM3 curves beyond existing follow-up using Robert). Given the data currently available this approach appears reasonable (although clearly subject to uncertainty due to the unknown prognostic implications of harbouring a BRAF mutation) and so was used in the base-case. It should be noted that any number of different sources of data could have been used for extrapolation of the limited data available from BRIM3 and that whilst this method is presented

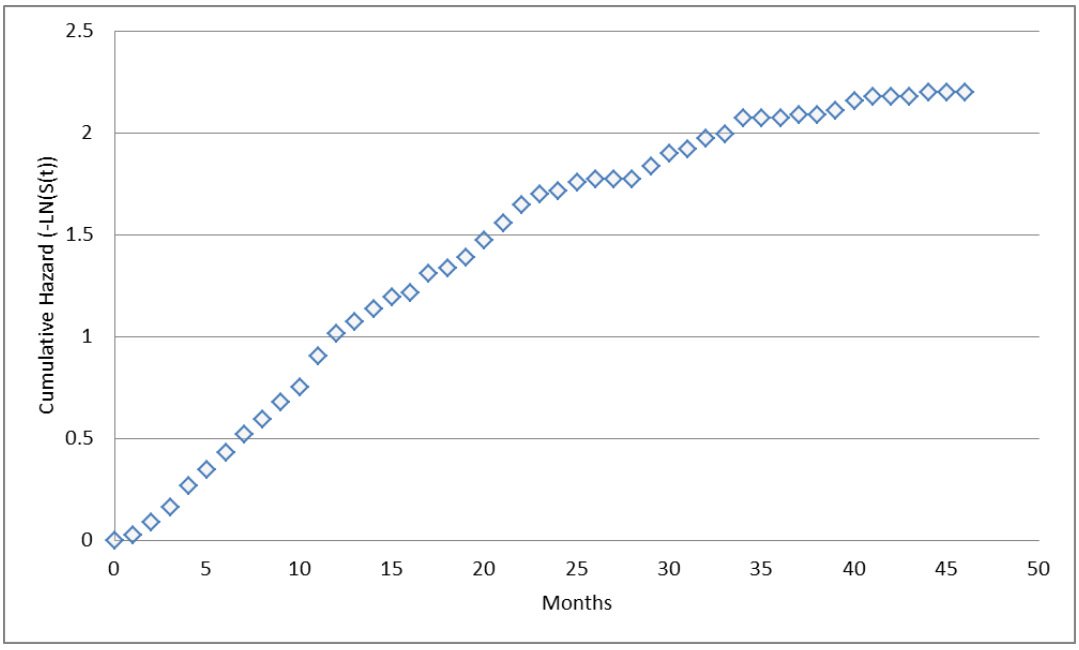
as a ‘base-case’ there are many other extrapolations that are equally plausible and only with longer term data will it become clear which is correct.

‘Tracing’ the Robert Hazard in order to model baseline risk if treated with dacarbazine

In order to allow the incorporation of the Robert hazard data into the model the dacarbazine OS curve from the Robert 2011 was digitised using TechDig.

The resultant KM curve was then converted into a cumulative hazard plot and assessed. Figure 47 below shows the resultant cumulative hazard plot.

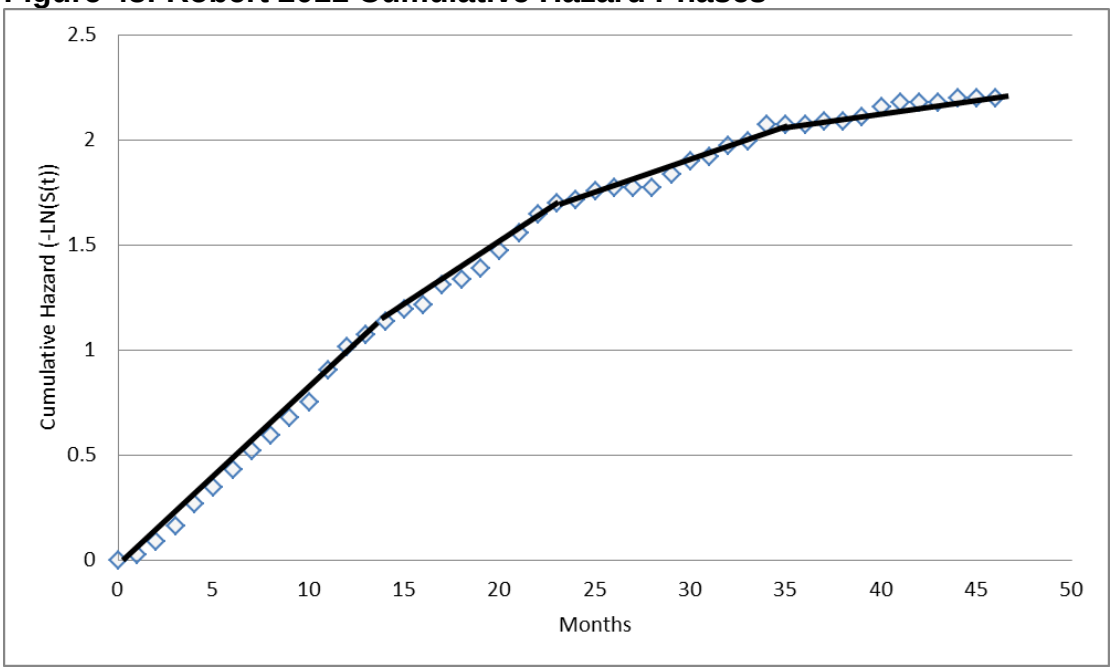
Figure 47: Robert 2011 Cumulative Hazard Plot



This cumulative hazard plot indicates that when treated with dacarbazine the hazard of death appears to be fairly constant from month 0 to month 14 (something suggested by the data currently available from BRIM3) and then flattens periodically from that point onwards (something that BRIM3 has not yet shown – potentially due to it having less than 14 months follow-up)

As the Robert dacarbazine hazard appeared to decline in a step-wise, rather than smooth manner (i.e. it features a series of 'kinks' at which the slope of the curve reduces) the cumulative hazards plot was split into 4 defined phases to which 4 individual linear functions could be fitted. These phases are shown in Figure 48 below.

Figure 48: Robert 2011 Cumulative Hazard Phases



The phases utilised and resultant monthly hazards estimated are as follows:

Table 31: The Robert hazards

	Start (month)	End (month))	Monthly Hazard	Weekly Hazard	R^2 Value of fitted function
Phase 1	0	14	0.086	0.019861432	0.9936
Phase 2	14	23	0.0658	0.015196305	0.9848
Phase 3	23	35	0.0328	0.007575058	0.9563
Phase 4	35	46	0.0141	0.003256351	0.9246

Whilst it may be argued that the cumulative hazard plot could have been fitted with a single non-linear function (capable of allowing the hazard to decline beyond the period of the study) the use of a function such as this would not change the results of the model significantly as the hazards derived based

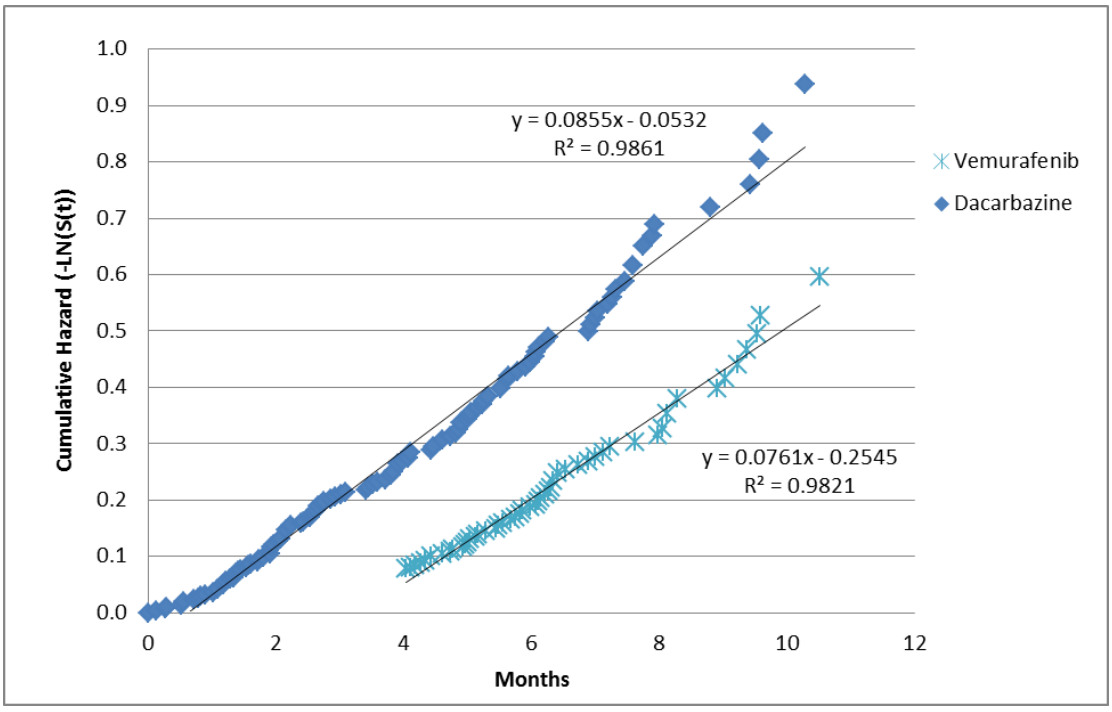
upon the phases are not extrapolated beyond year 4 of the study (i.e. they merely serve to 'trace' the hazard from Robert rather than informing longer term extrapolation).

Synthesising BRIM3 and Robert in order to derive a baseline risk curve

Following the 'tracing' detailed above the BRIM3 and Robert dacarbazine data were then synthesised to generate a dacarbazine OS curve for month 0-46 as follows:

1. The BRIM3 March 2011 dacarbazine OS data was utilised directly for as long as it appeared reliable. This appeared to be at 9.5 months (41 weeks) (the last point of convergence between the fitted exponential function and the KM curve).

Figure 49: BRIM3 OS Cumulative Hazard Plot (March 2011)



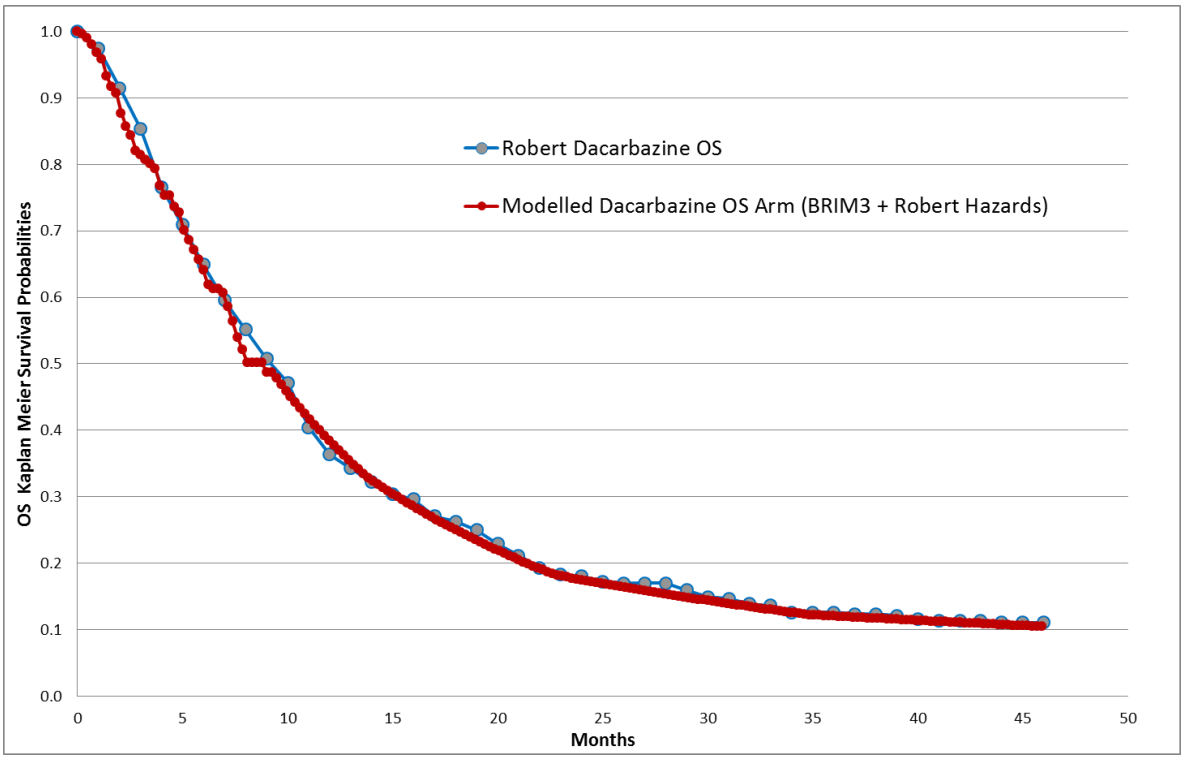
2. The stabilised hazard observed (0.0855 monthly hazard) in the March 2011 cut was then extrapolated out to month 14 of the model. Month 14

was chosen as the end of this hazard period as this was the point at which the Robert hazard appeared to ‘kink’ for the first time.

3. The hazards derived in phase 2,3 and 4 of Robert were then applied from month 14 – 46 of the dacarbazine arm

Figure 50 below demonstrates the face validity of the baseline risk curve modelled using the above technique (red line) compared to the observed Robert data (blue line).

Figure 50: Modelled dacarbazine arm vs Robert dacarbazine arm (OS KMs)



Completing the baseline risk curve

As the Robert data ended at months 46 it was necessary to apply further extrapolation to the tail of the simulated baseline risk curve.

In the base-case this was done by calibrating the hazard used in the model so that the 10-year survival landmark form the SEER registry (9.1% alive) was

reflected in the model (i.e. trial and error was utilised until a hazard which resulted in 9.1% of dacarbazine patients being alive at 10 years was estimated) (monthly hazard derived = 0.001905) .

In order to ensure that the impact of natural mortality was captured appropriately an 'IF' statement was placed in the model so that if the risk of death associated with age/gender adjusted background mortality was higher than the hazard derived based upon the SEER 10 year landmark figure background mortality would be used in the model.

This was then extrapolated out for the period of the time horizon (30 years) in order to simulate an OS curve for a patient receiving dacarbazine first line.

The SEER rather than Balch data was utilised in the base-case as this provided a single 10 year landmark figure for all stage IV patients whilst the Balch data provided landmarks by stage IV patients with different characteristics. The use of alternative longer term hazards was tested in sensitivity analysis.

Integrating an intervention arm

A vemurafenib arm was then incorporated into the model as follows:

1. The BRIM3 March 2011 vemurafenib OS data was utilised directly for as long as it appeared reliable. This appeared to be at 9.5 months (41 weeks) (the last point of convergence between the fitted exponential function and the KM curve (see Figure 49 above)).

2. The stabilised hazard observed (0.0761 monthly hazard) in the March 2011 cut was then extrapolated out to month 14 of the model. Month 14 was chosen as the end of this hazard period for the same reason as cited for the dacarbazine arm

3. From month 14 onwards it was assumed that vemurafenib provided no further treatment effect and the hazards applied in the dacarbazine arm

were similarly used in the vemurafenib arm (i.e. the HR from month 14 in the model is 1). The treatment effect associated with vemurafenib was limited to 14 months as it was felt to be optimistic to continue this treatment effect indefinitely and month 14 was the point that the Robert dacarbazine hazard 'kinked' for the first time.

Resultant OS KM Curves/Cumulative Hazard Plots

Figure 51, Figure 52 and Figure 53 below demonstrate the OS cumulative hazard plots produced using the above method.

Figure 51: Modelled OS Cumulative Hazard Plot (Month 0-23)

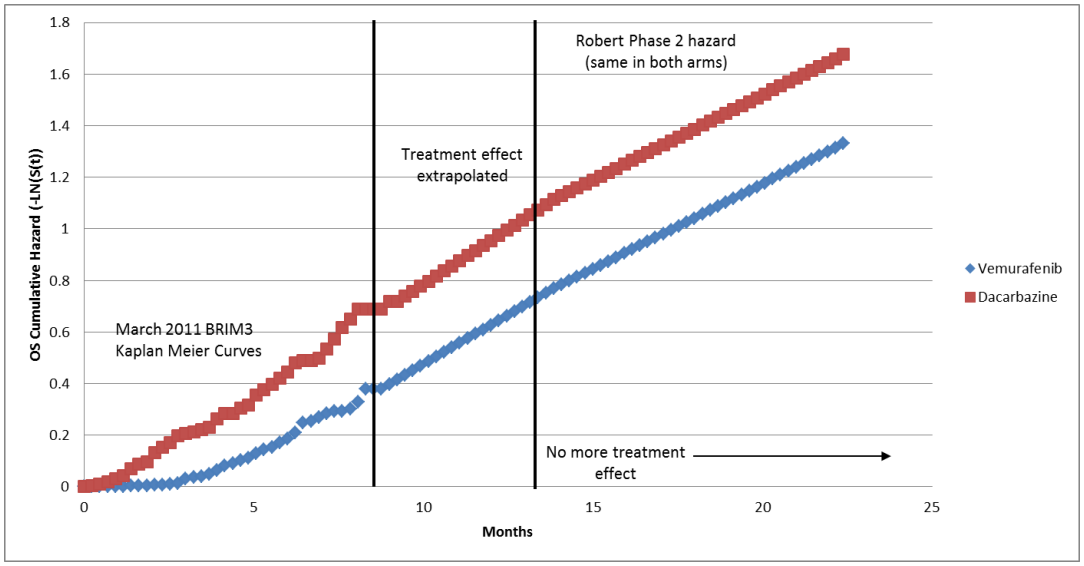


Figure 52: Modelled OS Cumulative Hazard Plot (Month 0-46)

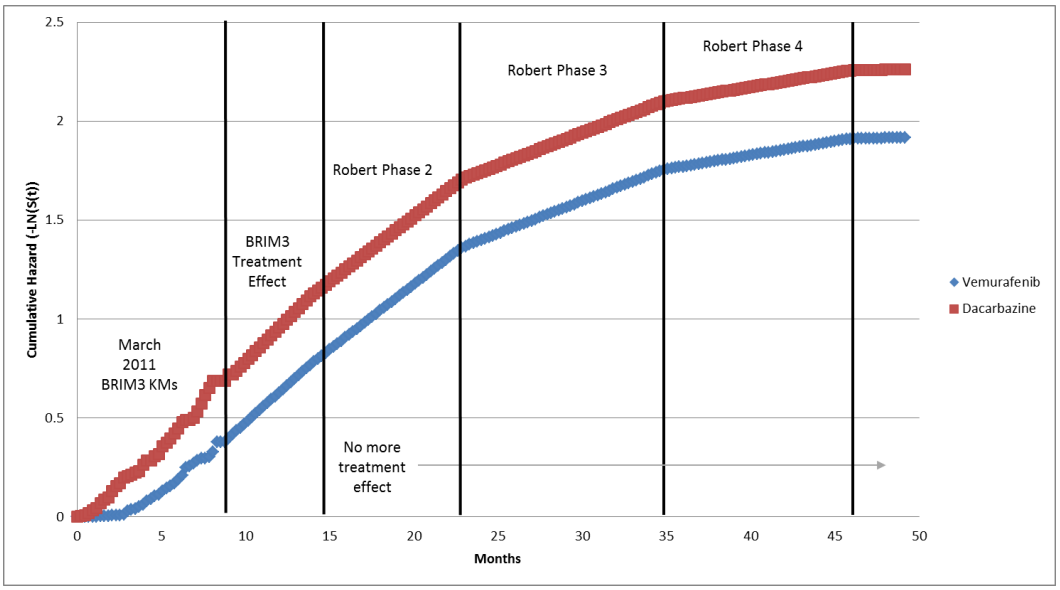


Figure 53: Modelled OS Cumulative Hazard Plot (Month 0-120)

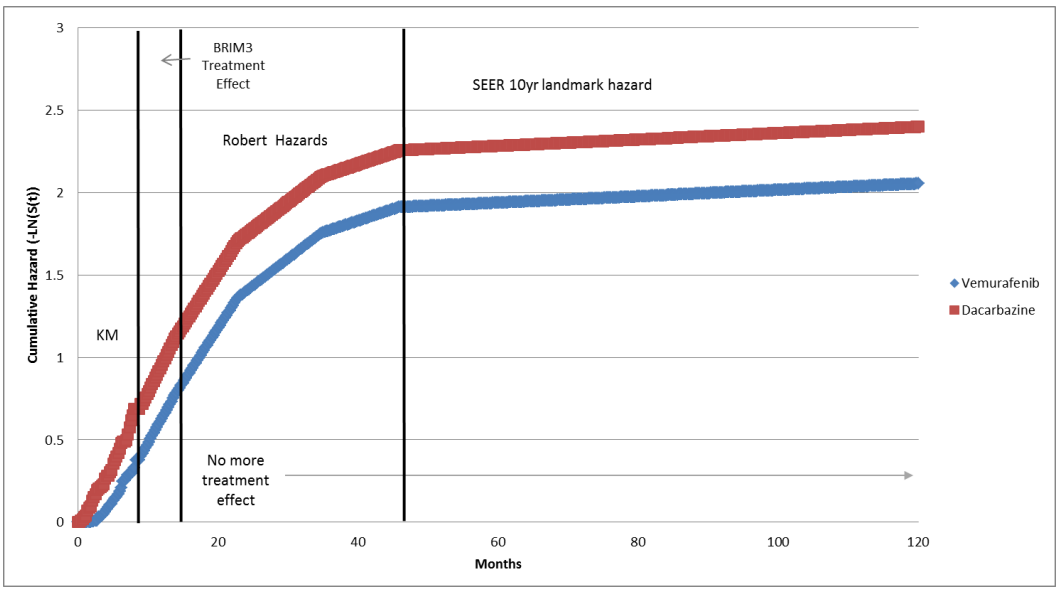


Figure 54 below demonstrates the OS KM curves produced using this method. The SEER registry curves (Figure 55) are reproduced below the base-case extrapolation in order to show the face-validity of the modelled curves relative to this long term real-world data.

Figure 54: Modelled OS KM Plot (Month 0-120)

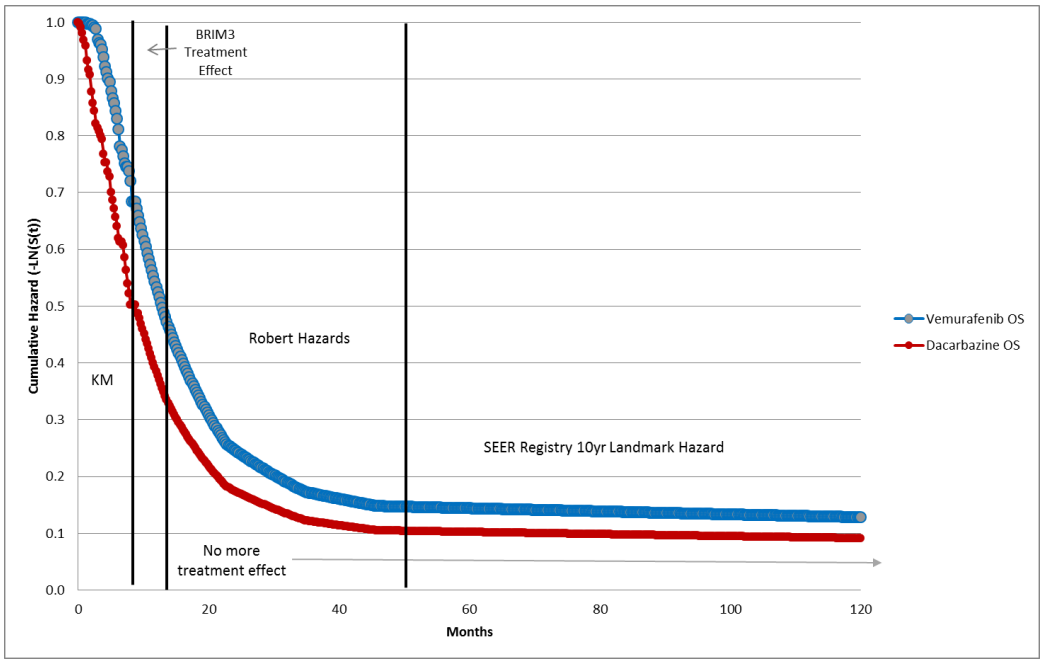
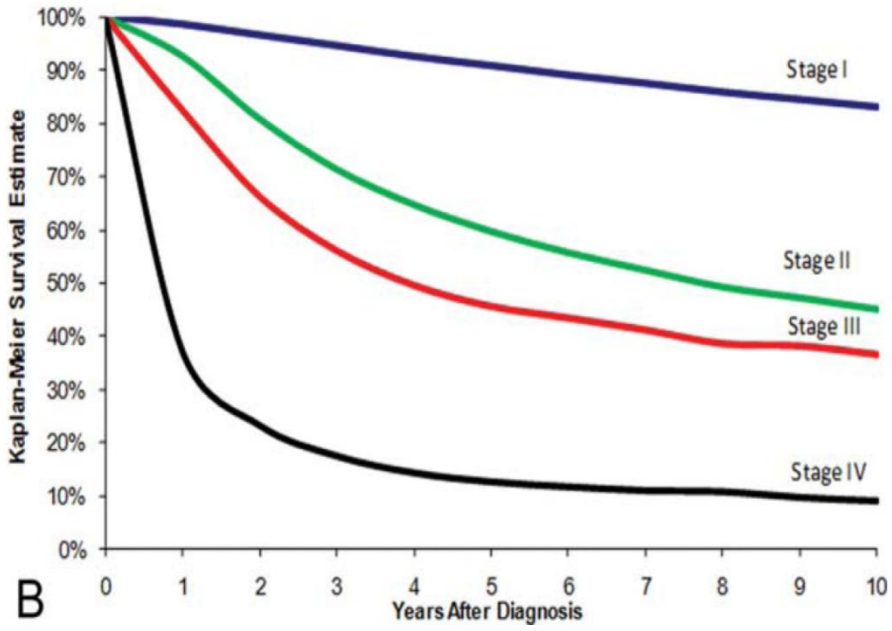


Figure 55: SEER registry OS curves (Xing 2010)

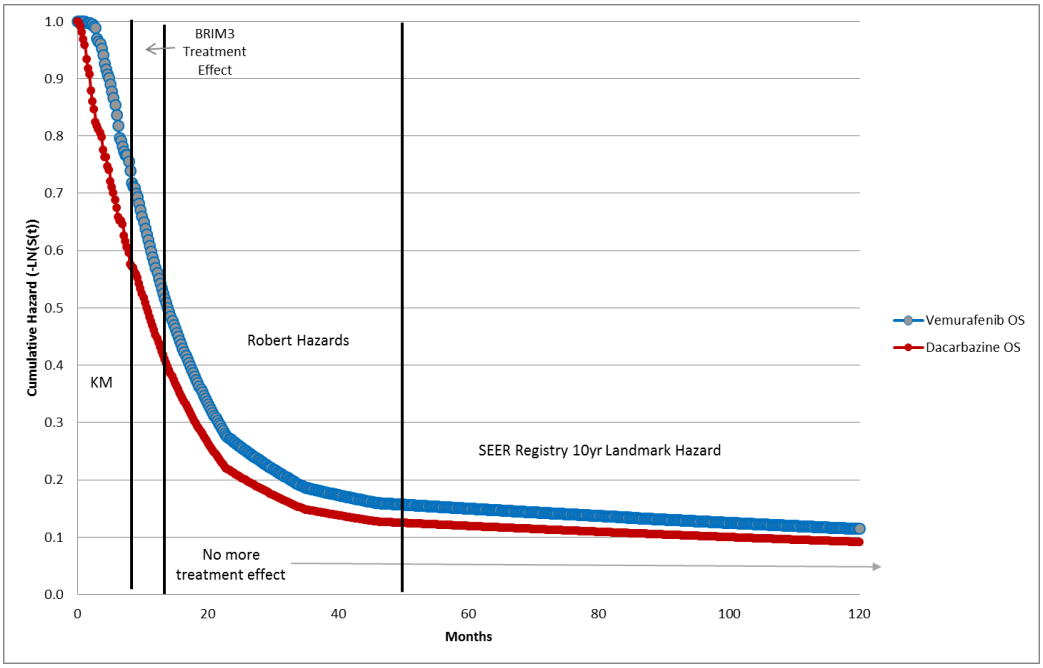


Whilst the extrapolation of 12 months of overall survival data out to the time horizons that appear to be required in modelling advanced melanoma is inherently associated with uncertainty, the use of the BRIM3 data augmented

by the Robert data and the SEER registry landmark figure appears one potentially reasonable way of doing this. However as there are clearly numerous other ways that this data could be modelled it is important to consider the ICERs produced using these alternative approaches when assessing the cost-effectiveness of vemurafenib.

Figure 56 below demonstrates the OS curves generated by repeating the base-case analysis with the crossover confounded October BRIM3 data rather than March data being used (with the SEER registry landmark hazard and initial BRIM3 treatment effect hazards recalculated).

Figure 56: October 2011 Cut Sensitivity Analysis OS KM Plot (Month 0-120)



The cost-effectiveness implications of using this extrapolation rather than the March cut are presented in section 6.7.7. below.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Please see 6.3.1. The weekly hazards estimated using Robert and SEER and displayed in the section above in addition to the monthly hazards derived from BRIM2 and used between approximately month 9 and month 14 of the model. Each of these hazards was converted into weekly probabilities prior to inclusion in the model.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

See above. There is reasonably strong evidence in a BRAF mutation status unspecific metastatic melanoma population that the risk of death appears to decline over time. This is integrated into the base-case modelling via use of the control arm of the Robert 2011 study and the use of data from the SEER registry.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No. PFS and OS were modelled individually and no relationship between the two was specified

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Clinical experts were consulted in two advisory boards in the development of the submission/model. These clinical experts were asked their opinion on the validity of the extrapolation conducted given their specialist knowledge of the subject. These clinicians noted extrapolation based upon BRIM3 alone would reach the x-axis much quicker than in the majority of melanoma overall survival data sets and so supported the use of the extrapolation approach taken.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 32: Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Transition Probabilities			
PFS monthly hazard in vemurafenib PFS curve tail	0.2087	-	Section 6.3.1.
PFS monthly hazard in dacarbazine PFS curve tail	0.2437	-	Section 6.3.1.
OS monthly hazard for vemurafenib (month 9 – 14)	0.0761	-	Section 6.3.1.
OS monthly hazard for dacarbazine (month 9 – 14)	0.0855	-	Section 6.3.1.
OS monthly hazard both model arms (month 14 – 23)	0.0658	-	Section 6.3.1.
OS monthly hazard both model arms (month 23 – 35)	0.0328	-	Section 6.3.1.
OS monthly hazard both model arms (month 35 – 46)	0.0141	-	Section 6.3.1.
OS monthly hazard both model arms	0.001905	-	Section 6.3.1.

(month 46 onwards)			
Utility Values			
Progression Free Survival (Response)	0.85	0.833, 0.867 (normal)	Section 6.4.9
Progression Free Survival (Stable Disease)	0.77	0.755, 0.785 (normal)	Section 6.4.9
Progressed Disease	0.59	0.578, 0.602 (normal)	Section 6.4.9
Skin reaction (Rash)	-0.03	-0.0296, -0.0304 (normal)	Section 6.4.9
Neutropenia	-0.08973	-0.088, -0.092 (normal)	Section 6.4.9
Costs			
Pharmacy costs per dispensing date (vemurafenib and dacarbazine)	£13	£6.63, £19.37 Gamma distribution applied under assumption standard error (SE) was a quarter of base case value.	Section 6.5.5
BRAF testing cost (per test)	£95	N/A	Section 6.5.5

Progression Free Survival Best Supportive Care	£378 per month	£192.78, £563.22 Gamma distribution applied under assumption standard error (SE) was a quarter of base case value.	Section 6.5.6
Progression Disease Best Supportive Care	£378 per month	£192.78, £563.22 Gamma distribution applied under assumption standard error (SE) was a quarter of base case value.	Section 6.5.6
Terminal Care Cost	£5,408 one off	£2,755, £8,047 Gamma distribution applied under assumption standard error (SE) was a quarter of base case value.	Section 6.5.6
Cost on disease progression	£648 one off	£330.48, £965.52 Gamma distribution applied under assumption standard error (SE) was a quarter of base case value.	Section 6.5.6
Palliative care (4 months before death)	£838 per month	£427.38, £1,248.62 Gamma distribution applied under assumption standard error (SE) was a quarter of base case value.	Section 6.5.6

Dacarbazine Administration	£248	£126.48, £369.52 Gamma distribution applied under assumption standard error (SE) was a quarter of base case value.	Section 6.5.5
Cost of Rash	£126.96	£64.75, £189.17 Gamma distribution applied under assumption standard error (SE) was a quarter of base case value.	Section 6.5.7
Cost of Neutropenia	£407.38	£207.76, £607.00 Gamma distribution applied under assumption standard error (SE) was a quarter of base case value.	Section 6.5.7
Cost of cuSCC/ keratocanthoma	£115	£58.65, £171.35 Gamma distribution applied under assumption standard error (SE) was a quarter of base case value.	Section 6.5.7
Cost per pack of vemurafenib	£1,750	N/A	Section 6.5.5
Cost per dose of dacarbazine	£63.60	Could technically be varied using PSA on BSA but given very low cost this functionality has not been	Section 6.5.5

		implemented in the model.	
General Parameters			
Age	54 years		BRIM3 RCT
BRAF mutation rate	48%		Long 2010
Response Rate (Vemurafenib)	48.4%	42%, 55% (normal)	BRIM3 RCT
Response Rate (Dacarbazine)	5.5%	3%, 9% (normal)	BRIM3 RCT
CI, confidence interval			

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

See section 6.3.1 for details of how extrapolation was conducted and the presentation of KM curves. The key assumptions underlying the OS extrapolation conducted are listed in section 6.3.8. below.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumption 1: Vemurafenib has no more treatment effect beyond month 14 of the model

Justification for assumption 1: It appears unreasonable to attempt to claim that the treatment effect observed for vemurafenib continues indefinitely. Month 14 was chosen as the point to end the treatment effect observed as that was the point at which the hazard in the Robert 2011 'kinked' for the first time. This assumption was relaxed in sensitivity analysis.

Assumption 2: From month 14 onwards the hazard of death expected to be observed in a BRAF mutation positive patients treated with either dacarbazine or vemurafenib are as observed in the Robert 2011 study control arm (month 14 – 46) and in the SEER registry (month 46 onwards).

Justification for assumption 2: There is currently a paucity of evidence with which to inform long term projective modelling of the BRIM3 data. The Robert 2011, Bedikian 2011 and SEER registry data indicates that in a general melanoma population the hazard of death appears to decline over time. As the first 12 months of the BRIM3 OS dacarbazine arm data appear indistinguishable from the dacarbazine data from Robert and Bedikian for the same period it appears reasonable to assume that they will similarly be indistinguishable after the period data are currently available from the BRIM3 study.

As there are a range of alternative assumptions that could be made when extrapolating the BRIM3 data it is important to consider the cost-effectiveness implications of testing alternative assumptions. OS sensitivity analysis is detailed further in section 6.6.2.

Assumption 3: If a patient is taking:

- 8 or 7 tablets of vemurafenib per day 4 packs (4 weeks supply) will be dispensed to them for every 28 days they remain in PFS.
- 6 or 5 tablets of vemurafenib per day 3 packs (4 weeks supply) will be dispensed to them for every 28 days they remain in PFS.
- 4 or 3 tablets of vemurafenib per day 2 packs of vemurafenib (4 weeks supply) will be dispensed to them for every 28 days they remain in PFS.
- 2 or 1 tablets of vemurafenib per day 1 pack of vemurafenib (4 weeks supply) will be dispensed to them for every 28 days they remain in PFS.

Justification for assumption 3: Assumption based upon the opinion of clinical experts. Patients will only be dispensed enough vemurafenib so that they do not ‘run out’ of tablets prior to their next dispensing date.

6.4 Measurement and valuation of health effects.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients’ quality of life.

Quality of life will be determined by the symptoms that a patients experiences. This is dictated by the site to which the melanoma has metastasised. It should be noted that melanomas may spread rapidly but "silently," and so patients may remain asymptomatic until a certain degree of damage has been done to the target organ where the metastatic deposit has developed. The most common sites of metastasis include the lymph nodes, other areas of the skin, fat and muscle, lungs, liver, brain and bone. Spread to the brain is associated with a worse prognosis. Therefore symptoms affecting patients may include

swollen lymph nodes, unexplained weight loss, chronic cough, headaches and seizures. Spread to the bowel may present as bowel perforation.

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

As the severity of the spread of the disease increases, the severity of the symptoms associated with the site of metastasis will also worsen, leading to deterioration of the patient. For example, early spread of melanoma to the brain may not be apparent. However, as the disease progresses, there may be the development of headaches with worsening intensity. Seizures, cranial nerve palsies and visual changes may develop with progressive disease. It is possible that cognitive function may also be disrupted with the subsequent development of confusion. Since this can have a debilitating effect of a patient's ability to carry out activities of daily living, it is entirely likely that their quality of life will suffer, and that they may require further social and psychosocial support.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.

- Results with confidence intervals.

FACT-M data was collected in BRIM3 however completion rates were extremely low (particularly following the reporting of the interim analysis results) and so this data has never been reported. FACT-M is not preference based and does not conform to the reference case.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Mapping was not conducted. The utility values utilised in the base-case modelling were those derived by Beusterien et al (as identified in the on-going NICE appraisal of ipilimumab in metastatic melanoma) with additional adverse event disutilities incorporated into the model.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), EconLIT and NHS EED were searched for studies assessing utility values for different health states in metastatic melanoma. The search was designed to evaluate all potentially relevant utility scores that have been used in metastatic melanoma health technology evaluations. The complete search strategy is provided in

section 9.10. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Keyword strategies were developed using key references retrieved through initial scoping searches. As a similar search was conducted by the manufacturer of ipilimumab in support of their ongoing STA the search conducted was not completely *de novo* but an update of that search designed to identify any newly published utility values (with the search therefore limited from 9th December 2010 – the date the ipilimumab search was conducted).

The search was conducted using Dialogue ProQuest as a search client for EMYY, EMBA and MEYY (accessed on 17th January 2012) whilst NHS EED was searched using The Centre for Reviews and Dissemination's website (University of York 2011) and ECON LIT was searched (The American Economic Association & EconLIT 2011) both accessed on 19th January 2012. Each search result's title and abstract were assessed for relevance according to the pre-defined inclusion and exclusion criteria (see table below).

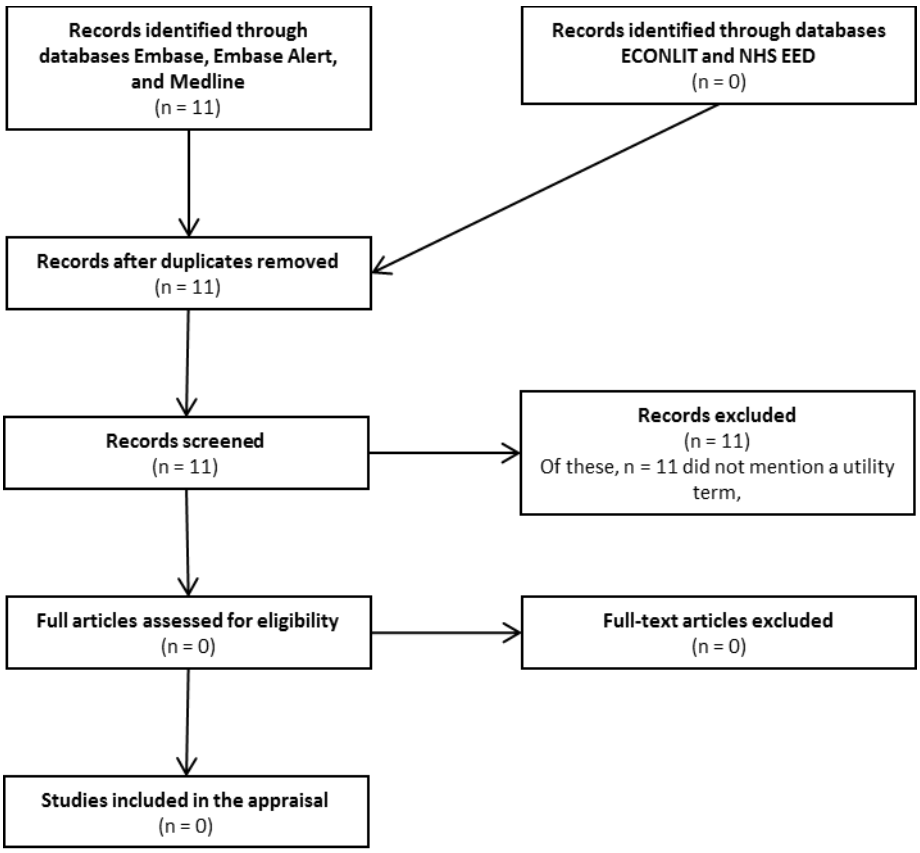
If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

Table 33: Utility search inclusion/exclusion criteria

Inclusion Criteria	Exclusion Criteria
Metastatic or advanced melanoma Health related quality of life QALY or quality adjusted life year SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL Utilities Time Trade Off or Standard Gamble	Review of studies already included Not QoL studies Utility value not elicited by the general public Not in metastatic/advanced setting No useful HRQoL/Utility values for economic modeling

In total 11 studies were identified through 5 databases. Of these, all 11 were excluded by the independent reviewers after reading the abstracts as they all failed to pass the criteria as detailed in Appendix 12.

Figure 57: PRISMA flow for utility search



6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.

- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

No new studies were identified.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

No new studies were identified.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

Vemurafenib has a largely manageable safety profile, with very few life-threatening adverse events. Most events may be dealt with using simple treatments e.g. analgesia for arthralgia, anti-emetics for nausea. Cutaneous squamous cell carcinomas may be removed with simple excision which can take place as a day-case procedure. Photosensitivity can be managed with sun protection creams and the wearing of close-weave clothing. While this may have cause some disruption to a patient's HRQL, it should be remembered that the burden of the metastatic disease, once it has affected the target organs, also cause considerable symptoms and deterioration to a patient's quality of life. Therefore the adverse events and subsequent management associated with vemurafenib do not meaningfully impact on a patient's HRQL, when put in the context of the severity of the disease.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

In the on-going appraisal of ipilimumab the following utility values were identified. No new values were identified following the updated search undertaken.

Table 34: Utility values identified in ipilimumab appraisal

Health State	Utility Value: Hodi EORTC QLQ-C30 mapped to EQ-5D	Utility Value: Hodi SF-36 mapped to EQ-5D	Utility Value: Beusterien et al (UK mean)
Progression Free Survival	0.80 {0.53; 0.97}	0.64	0.77
Progressed Disease	0.76 {0.46; 0.97}	0.62	0.59

Two of the three potential sources of utility data identified by the manufacturer of ipilimumab were based upon mapping of HRQoL data collected in the Hodi RCT (ipilimumab + gp100 vs gp100 vs ipilimumab) whilst one was a standard

gamble study conducted in the UK and Australia (featuring 140 participants of which 63 were from the UK).

The above utility values were presented to clinical experts who were asked to comment on whether they believed it was reasonable to apply values mapped from HRQoL data collected in patients receiving ipilimumab to vemurafenib or dacarbazine. These clinicians indicated that utilising the same PFS utility values for vemurafenib, dacarbazine and ipilimumab would significantly understate the benefits of vemurafenib in providing rapid response and reduction of tumour burden. They noted that whilst a patient could technically be in 'PFS' with either treatment they would expect a greater utility value for patients receiving vemurafenib than the other two treatments as the response rates observed with vemurafenib are so much higher than for dacarbazine of ipilimumab (response rate in BRIM3 vemurafenib arm was 8.8 times higher than in the dacarbazine arm (48.4% vs 5.5%)). When notified that the Beusterien study also featured a PFS utility value specific to patients experiencing a response to treatment (0.85 compared to the 0.77 derived in patient with stable disease) the clinical experts suggested that those values should be utilised in order to derive utilities for each arm individually.

They also noted that it would probably be inappropriate to utilise a post-progression utility value derived from quality of life data taken from the Hodi study in a model investigating the cost effectiveness of dacarbazine as a first line treatment. The clinicians stated that some patients 'progressing' on ipilimumab (as defined by growth of their tumours) in fact experience late responses to treatment. It was felt that the relatively small difference between the PFS and PD utilities derived based upon the Hodi study may be due to the fact that some patients considered as 'progressed' in Hodi may in fact have returned to a 'progression free' health state due to delayed tumour shrinkage.

Given the opinions of the clinical experts it was determined that the Beusterien values should be utilised in order to derive base-case utility values with alternative values tested in sensitivity analysis.

In line with the costing of adverse events solely those AEs occurring at greater than 5% incidence at grade 3/4 were considered in the utility values derived. The potential disutility associated with lower grade toxicities was assessed in sensitivity analysis via the use of lower base-case utility values for both agents.

Table 35: Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
Progression Free Survival (Response)	0.85	0.833, 0.867	Section 6.4.9	UK standard gamble study that allows ability to differentiate PFS by response/stable disease
Progression Free Survival (Stable Disease)	0.77	0.755, 0.785	Section 6.4.9	UK standard gamble study that allows ability to differentiate PFS by response/stable disease
Progressed Disease	0.59	0.578, 0.602	Section 6.4.9	UK standard gamble study rather than values mapped from Hodi HRQoL data
Skin reaction (Rash)	-0.03	-0.0296, -0.0304	Section 6.4.9	AE occurring at greater than 5% incidence at grade 3/4. Beusterien disutility.
Neutropenia	-0.08973	-0.088, -0.092	Section 6.4.9	AE occurring at greater than 5% incidence at grade ¾.

				Nafees 2008 value.
Resultant PFS Utility Value (Vemurafenib)	0.806	No derived explicitly	Section 6.4.9	See below
Resultant PFS Utility Value (Dacarbazine)	0.767	No derived explicitly	Section 6.4.9	See below

Whilst keratocanthoma/cuSCC occurred at an incidence of greater than 5% at grade 3 severity in the vemurafenib arm of BRIM3 the clinical experts noted that this AE was not associated with a disutility and so this was not included in the model (although the cost of removing them was). The disutility associated with rash was taken from the Beusterien study whilst the disutility associated with neutropenia was taken from Nafees et al (a standard gamble study focused on the derivation of health state utility values and AE disutilities in mNSCLC) (clinical experts noted that they felt it was reasonable to utilize the disutility associated with neutropenia in mNSCLC in advanced melanoma).

The utility values above were combined in the following way in order to derive the base-case PFS utility values. Note that the incidence of grade 3/4 rash in the vemurafenib arm of BRIM3 was 8.33% whilst the incidence of neutropenia was 8.5% in the dacarbazine arm.

Vemurafenib

$$(0.85 * 0.484) + (0.77 * (1 - 0.448)) + (-0.03 * 0.0833) = 0.806$$

Dacarbazine

$$(0.85 * 0.550) + (0.77 * (1 - 0.550)) + (-0.08973 * 0.085) = 0.767$$

The use of different response rates and resultant utility values was assessed in sensitivity analysis (in particular the use of the values derived from the Hodi study).

Given the heterogeneous survival experience of advanced melanoma patients it questionable as to whether the progressed disease state can be modelled with a single utility value. It may be more appropriate to model the quality of life of the PD health state for longer-term melanoma survivors at a higher value than those for patients who experience extremely rapid disease progression and death. This was tested in sensitivity analysis via the application of the post-progression utility values estimated via mapping of HRQoL data from the Hodi RCT.

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

See the response to 6.4.9 above.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The PFS health state is designed to capture the relatively high quality of life period of a patients disease in which their tumor (and associated tumour burden) has stabilized or reduced in size. The response/stable disease utility weighting is designed to capture the difference in quality of life expected in a patient with a reduction in tumour size.

The PD health state is designed to capture the relatively poor quality of life period after a patient experiences disease progression.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Only AEs occurring at greater than 5% incidence at grade 3/4 are considered in the model. This decision was taken as attempting to include each event that occurred in BRIM3 irrespective of the severity of that AE would add a significant amount of complexity to the model with a relatively minor impact upon the model results.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

N/A.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Quality of life is assumed to be the same in each health state irrespective of how long a patient has been in that health state.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

See above. Resource identification, measurement and valuation

NHS costs

6.4.16 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

In order to remain consistent with the NICE appraisal of ipilimumab the majority of the non-treatment specific costs utilised in the vemurafenib model are the same as those used, and accepted by the ERG and Committee, in that technology appraisal.

6.4.17 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

See above.

Resource identification, measurement and valuation studies

6.4.18 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis

- technology costs.

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), NHS EED and Econ LIT were searched for studies assessing resource utilisation of patients with metastatic melanoma. The search was designed to evaluate all potentially relevant cost studies that have been used in advanced metastatic melanoma health technology evaluations, within the United Kingdom. The complete search strategy is provided in section 9.10. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Keyword strategies were developed using key references retrieved through initial scoping searches. The search was conducted from 9th December 2010 onwards to see if any (additional to those reported in the ongoing appraisal of ipilimumab) cost papers could be found. ProQuest was used to search EMYY, EMBA and MEYY (accessed on 17th January 2012) whilst NHS EED was searched using The Centre for Reviews and Dissemination's website (University of York 2011) and ECON LIT was searched (The American Economic Association & EconLIT 2011) both accessed on 19th January 2012. Each search result's title and abstract were assessed for relevance according to the pre-defined inclusion and exclusion criteria (see table below).

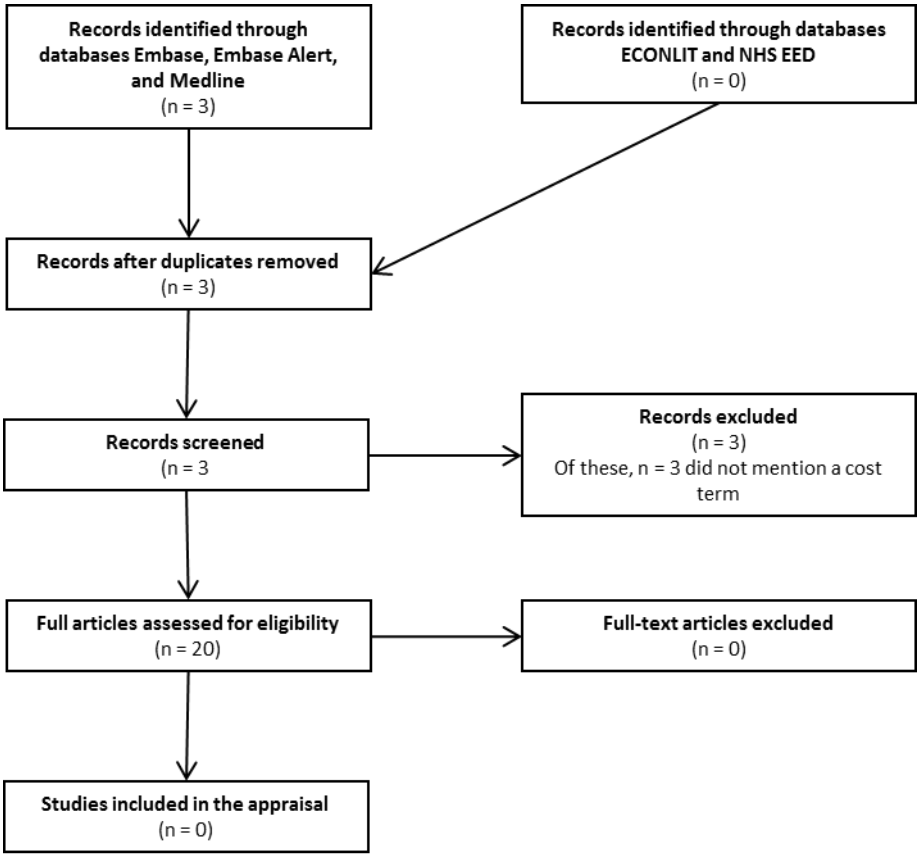
If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria:

Table 36: Inclusion and Exclusion Criteria for Resource Utilisation Studies

Inclusion criteria	Exclusion criteria
Advanced or metastatic melanoma patients Resource utilisation from a UK NHS perspective	Early melanoma patients Resource utilisation from a private/US setting – and any other non-UK country. Costs derived from studies more than 5 years old.

In total, 3 studies were identified thought 5 databases. Of these 3, all 3 were excluded by the independent reviewers based upon their abstracts as all 3 failed to meet the inclusion criteria as described in Appendix 13.

Figure 58: PRISMA flow-diagram for cost search



6.4.19 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

Clinical experts were asked to comment on the face-validity of the costs and resource used figures (where available) included in the model with a particular focus paid to the generalizability of the health state costs applied in the ongoing appraisal of ipilimumab (the only other NICE appraisal in advanced melanoma). Whilst the cost figures utilised for health states utilised in the

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

ipilimumab NICE appraisal are publicly available the resource use estimates underlying those costs remain academic in confidence and so it is not possible to assess how valid each of the costs used are for this appraisal.

However upon consultation the clinical experts noted that they would expect the health state costs employed in the ipilimumab appraisal to be appropriate for use in this appraisal as there was not likely to be significant difference between health state costs between the two (adverse event treatment aside – these were included separately in the model). Following this opinion and the fact that the health state costs used in the ipilimumab appraisal appeared to have been accepted by the ERG and Committee it was determined that the use of these figures would be reasonable in the base-case of the model.

Intervention and comparators' costs

6.4.20 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Table 37: Unit costs associated with the technology in the economic model

Items	Vemurafenib	Reference	Dacarbazine	Reference
Technology cost	£1,750 per pack (56 tabs)	Section 6.55	£63.60 per dose (given every 3 weeks)	BNF62, Section 6.55
Administration cost	N/A (oral therapy)	-	£248	NHS Reference Cost 2009/2010 - SB12Z - Deliver simple parenternal chemotherapy at first attendance (outpatient)
Pharmacy costs	£13 every 4 weeks	Section 6.55	£13 every 3 weeks	Section 6.55
BRAF Test	£95 per test (£197.92 per BRAF positive patient identified)	Section 6.55	N/A	-

Cost of vemurafenib

The cost of vemurafenib was included in the model utilising the 'dispensing date' approach used in previous NICE appraisals of oral oncology agents (NICE TA227, erlotinib for the first line treatment of EGFR M+ mNSCLC (ongoing)). Following consultation with clinical experts it was determined that

a patient would be dispensed vemurafenib every 28 days (4 weeks) with the patient given enough vemurafenib to last them for the next 28 days.

As vemurafenib is provided in packs of 56 tablets if a patient is taking 8 tablets a day this will require 4 packs of vemurafenib (56 * 4 = 224 = 7 * 8 * 4) to be dispensed every 28 days whilst if a patient is taking 7 tablets a day this will also require 4 packs to administered (as the patient requires 196 tablets but dispensing only 3 pack will give them only 168 and so 4 packs must be dispensed). Table 38 below demonstrates the dispensing date pack requirement/cost associated with a patient taking different numbers of tablets.

Table 38: Dispensing date pack requirements/costs

Tablets a day	Tablets required for 28 days	Minimum number of packs possible to dispense to patient	Cost per dispensing date
8	224	4	£7,000
7	196	4	£7,000
6	168	3	£5,250
5	140	3	£5,250
4	112	2	£3,500
3	84	2	£3,500
2	56	1	£1,750

1	28	1	£1,750

This approach was applied in the model by calculating an expected cost of dispensing vemurafenib based upon the doses patients received every 28 days.

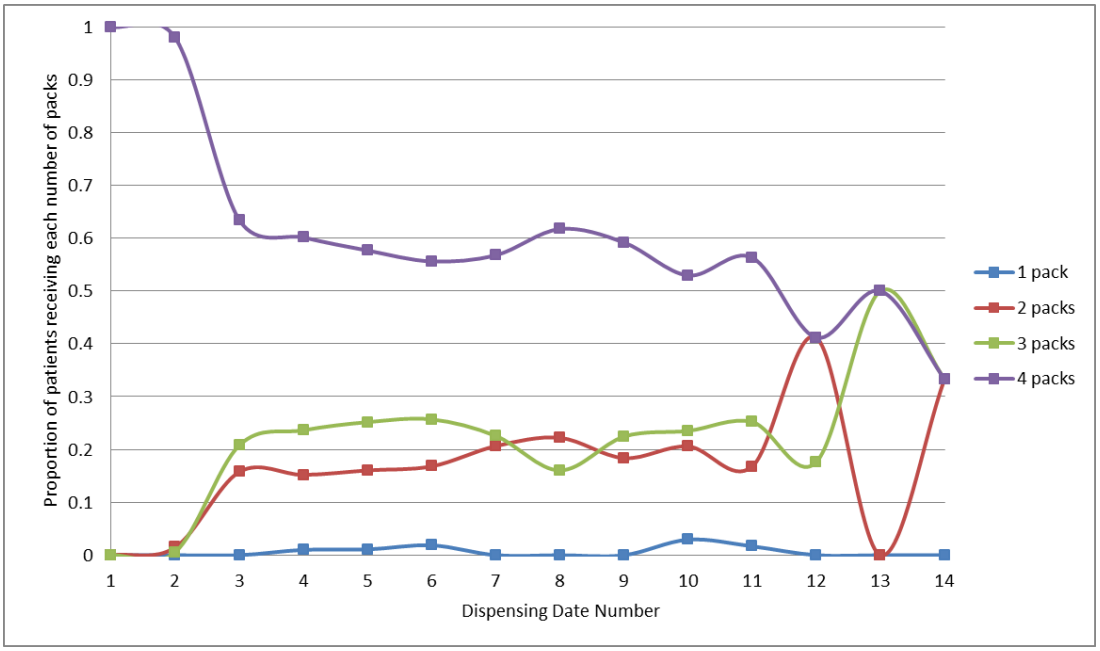
For example if 80% of patients on day 58 (the third dispensing date) received 8 tablets whilst 20% received 6 tablets the expected cost of vemurafenib per patient in PFS would be:

$$0.8 * £7,000 + 0.2 * £5,250 = £6,650$$

Note: the above figures are for demonstration purposes only.

The proportion of patients expected to be dispensed each number of packs on each of the dispensing dates is presented in Figure 59 below (proportions derived using above method and data on the doses received by patients on each of the dispensing dates in BRIM3):

Figure 59: Proportion of patients receiving each number of packs



These proportions were then combined with the costs in in order to derive the expected cost of vemurafenib from dispensing date 1 to 11. As the proportions became erratic from date 11 onwards (due to reducing patient numbers) it was assumed that in all future dispensing dates the average cost of vemurafenib modelled in dates 3 to 11 would be expected. The proportions observed on dispensing date 1 and 2 were not considered when modelling beyond follow-up as these appeared to be outliers and unrepresentative of the 'stabilised' proportions observed from date 3 onwards.

The expected cost of each dispensing date was then multiplied by the proportion of patients in PFS at that dispensing date (with no half cycle correction applied) in order to derive the expected cost of vemurafenib every 28 days. This was repeated for each dispensing date, discounted appropriately and then summed in order to derive the expected present value cost to the NHS of a patient taking vemurafenib.

Cost of dacarbazine

Dacarbazine is administered at a dose of 1,000mg/m^2. Mean BSA in BRIM3 was 1.9141m^2. The required dose for dacarbazine is therefore 1,9141mg every 3 weeks. Dacarbazine can be purchased in 1,000mg vials at a cost of £31.80 per vial (BNF62). The expected cost per dose of dacarbazine is therefore £63.60 (2 x 1,000mg vials).

Whilst consideration of distribution of BSA around the mean value would produce a more accurate expected cost of dacarbazine given the low cost involved solely the mean value was used in the model. This cost was then applied to the proportion of patients in PFS at the start of each 3 week period in order to estimate the cost of dacarbazine (note: no half cycle correction applied as the NHS must still pay for dacarbazine administered even if a patient progresses prior to the next cycle).

Pharmacy costs

In 2008 a prospective time-and-motion study was conducted in two UK secondary care NHS Trusts to quantify, in terms of time, the secondary care NHS resource use associated with the preparation and administration of XELOX (capecitabine in combination with oxaliplatin) and FOLFOX-6 (5-FU in combination with folinic acid and oxaliplatin) in metastatic colorectal cancer (Millar 2008). The results of the study indicated that dispensing of capecitabine (an oral agent) required an average of 12 minutes. Therefore for the base-case it was assumed that the dispensing of vemurafenib would similarly take 12 minutes.

One hour of a pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £65 (PSSRU, 2010). It was therefore estimated in the base case that the cost of dispensing vemurafenib every 28 days was £13 (65*12/60).

In the same study (Millar 2008) it was found that dispensing oxaliplatin (an IV administered chemotherapy) similarly took 12 minutes. In the base-case it was therefore assumed that dacarbazine would take 12 minutes to dispense every 3 weeks at a cost of £13.

Administration costs

As vemurafenib is an oral product its administration does require access to a hospital chemotherapy suite nor reconstitution in a pharmacy asceptic unit. Vemurafenib simply requires a pharmacist to dispense and check a prescription every 28 days with no further cost to the NHS. Vemurafenib is therefore a relatively cheap treatment to administer compared to IV administered dacarbazine.

Dacarbazine is IV administered and so requires chemotherapy suite chair time to be administered. This was included in the model via use of NHS Reference

Cost SB12Z - Deliver simple parenternal chemotherapy at first attendance (outpatient) (NHS Reference Cost 2009/2010) applied every three weeks that patients spent in the dacarbazine arm PFS health state.

BRAF testing costs

As vemurafenib is indicated for solely BRAF V600 mutated patients, if NICE approved, BRAF mutation testing of all potentially eligible advanced melanoma patients must become standard clinical practice. BRAF mutation testing is not currently undertaken widely in the NHS and so this testing requirement is associated with an incremental cost.

There is one CE approved BRAF mutation test available (the 'cobas' test produced by Roche diagnostics). This was the mutation test utilized in the BRIM3 trial (ensuring that the results of the study should be transferable to UK clinical practice with no concerns about any difference between the characteristics of tests used in clinical practice compared to clinical trials). A single BRAF test will cost £95 per patient tested (Roche diagnostics 2012) which equates to a cost of £197.92 per BRAF positive patient identified (using 48% mutation rate (Long 2010). This cost was applied to solely the vemurafenib arm of the model.

Health-state costs

6.4.21 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

Table 39: List of health states and associated costs in the economic model

Health states	Value	Reference
Progression Free Survival Best Supportive Care	£378 per month	Value as per on-going STA of ipilimumab
Progression Disease Best Supportive Care	£378 per month	Value as per on-going STA of ipilimumab
Terminal Care Cost	£5,408	Value as per on-going STA of ipilimumab
One off cost on disease progression	£648	Value as per on-going STA of ipilimumab
Palliative care (4 months before death)	£838 per month	Value as per on-going STA of ipilimumab

The costs detailed above are those applied in the ongoing NICE appraisal of ipilimumab. As these costs appear to have been accepted by the ERG and Committee in that appraisal and clinical experts indicated that it was reasonable to assume the above costs were also applicable to vemurafenib these values were used in the base-case.

As the model runs on a weekly cycle length the monthly costs were split into weekly costs prior to being applied in the model. In order to make the model simpler the palliative care cost was applied as one lump sum upon death (£3,352).

Adverse-event costs

6.4.22 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

All adverse events occurring in greater than 5% at grade 3/4 severity in either arm of BRIM3 were considered in the modelling undertaken. Three adverse events met this requirement; Rash (8.33% in vemurafenib arm), Neutropenia (8.5%in dacarbazine arm) and cuSCC/Keratocanthoma (14.29% in vemurafenib arm). The costs associated with each of these adverse events were included in the model utilising values from previous NICE technology appraisals and NHS Reference Costs 2009/2010. These costs are detailed in Table 40 below.

Table 40: List of adverse events and summary of costs included in the economic model

Adverse events	Value	Reference
Rash	£126.96	Roche 2006 uplifted using PSSRU HCHS inflation index
Neutropenia	£407.38	Roche 2006 uplifted using PSSRU HCHS inflation index
cuSCC/ keratocanthoma	£115	NHS Reference Costs 2009/2010 – JC03C: Outpatient major skin procedure category 1 without CC)

Miscellaneous costs

6.4.23 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

All costs included in the model are detailed above.

6.5 Sensitivity analysis

6.5.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Structural sensitivity analysis was focused upon understanding the cost-effectiveness implications of choosing alternative forms of extrapolation for the overall survival data within the model. These are detailed in Table 42 below.

6.5.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Table 41: Parameters varied in deterministic sensitivity analysis

Parameter	Base-Case Value	Low Value	High Value
Transition Probabilities			
Monthly hazard of disease progression after month 9 (vemurafenib) – note: KM used before this point in time.	0.2087	-10%	+10%
Monthly hazard of disease progression after month 7 (dacarbazine) - note: KM used before this point in time.	0.2437	-10%	+10%
Monthly hazard of death between month 9 and month 14 (vemurafenib). note: KM used before this point in time.	0.0761	-10%	+10%
Monthly hazard of death between month 9 and month 14 (dacarbazine). note: KM used before this point in time.	0.0855	-10%	+10%
Monthly hazard of	0.0658		

death between month 14 and month 23 (both arms		-10%	+10%
Monthly hazard of death between month 23 and month 35 (both arms	0.0328	-10%	+10%
Monthly hazard of death between month 35 and month 46 (both arms	0.0141	-10%	+10%
Monthly hazard of death from month 46 onwards - note: model includes IF statement linked to age/gender adjusted background mortality so that highest rate of this figure and background mortality is used in model	0.00195	-50%	+50%
Utility Values			
Progression Free	0.85		

Survival (Response)		-10%	+10%
Progression Free Survival (Stable Disease)	0.77	-10%	+10%
Progressed Disease	0.59	-10%	+10%
Skin reaction (Rash)	-0.03	-10%	+10%
Neutropenia	-0.08973	-10%	+10%

Costs			
Pharmacy costs when vemurafenib dispensed	£13	£6.63 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£19.37 (Upper confidence interval if standard error = 1/4 base case value (assumption))
Dacarbazine Pharmacy Cost	£13	£6.63 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£19.37 (Upper confidence interval if standard error = 1/4 base case value (assumption))
Dacarbazine Administration Cost	£248	£126.48 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£369.52 (Upper confidence interval if standard error = 1/4 base case value (assumption))
Monthly PFS BSC Cost	£378	£192.78 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£563.22 (Upper confidence interval if standard error = 1/4 base case value (assumption))
		£192.78	£563.22

Monthly PD BSC Cost	£378	(Lower confidence interval if standard error = 1/4 base case value (assumption))	(Upper confidence interval if standard error = 1/4 base case value (assumption))
Terminal Care Cost	£5,401	£2,754.51 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£8,047.49 (Upper confidence interval if standard error = 1/4 base case value (assumption))
Cost of Rash	£126.96	£64.75 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£189.17 (Upper confidence interval if standard error = 1/4 base case value (assumption))
Cost of Neutropenia	£407.38	£207.76 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£607.00 (Upper confidence interval if standard error = 1/4 base case value (assumption))
Cost of cuSCC/ keratocanthoma	£115	£58.65 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£171.35 (Upper confidence interval if standard error = 1/4 base case value (assumption))

Patient Characteristics			
Age	54	45	65
BRAF mutation incidence	48%	40%	60%
General Parameters			
Time Horizon	30 years	20 years	-
Costs Discount Rate	3.5%	0%	6%
Health Outcomes Discount Rate	3.5%	0%	6%
Both Discount Rates	3.5%	0%	6%

In addition to the above, further analyses investigating the impact of utilising different extrapolations of overall survival was tested. These are presented below.

Table 42: OS Sensitivity Analyses Conducted

Scenario	Description
1	Base-Case (March 2011 BRIM3 cut + Robert data + SEER 10yr landmark hazard/background mortality (highest chosen), HR= 1 from month 14 onwards)
2	October Cut (Oct 2011 BRIM3 cut + Robert data + SEER 10yr landmark hazard/background mortality (highest chosen), HR= 1 from month 14 onwards)
3	Base-Case with longer treatment effect (March 2011 BRIM3 cut + Robert data + SEER 10yr landmark hazard/background mortality (highest chosen), HR= 1 from month 35 onwards (time all patients ceased treatment with vemurafenib)

The OS curves estimated using the above approaches are displayed below:

Figure 60: OS Scenario 1 – Base Case

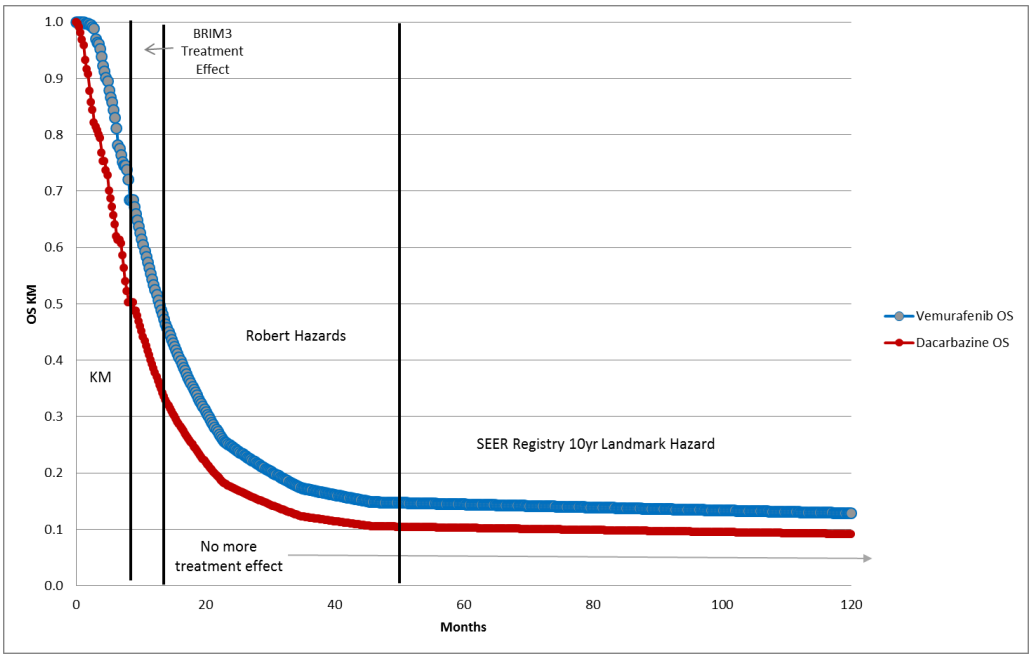


Figure 61: OS Scenario 2 – October cut (24% crossover)

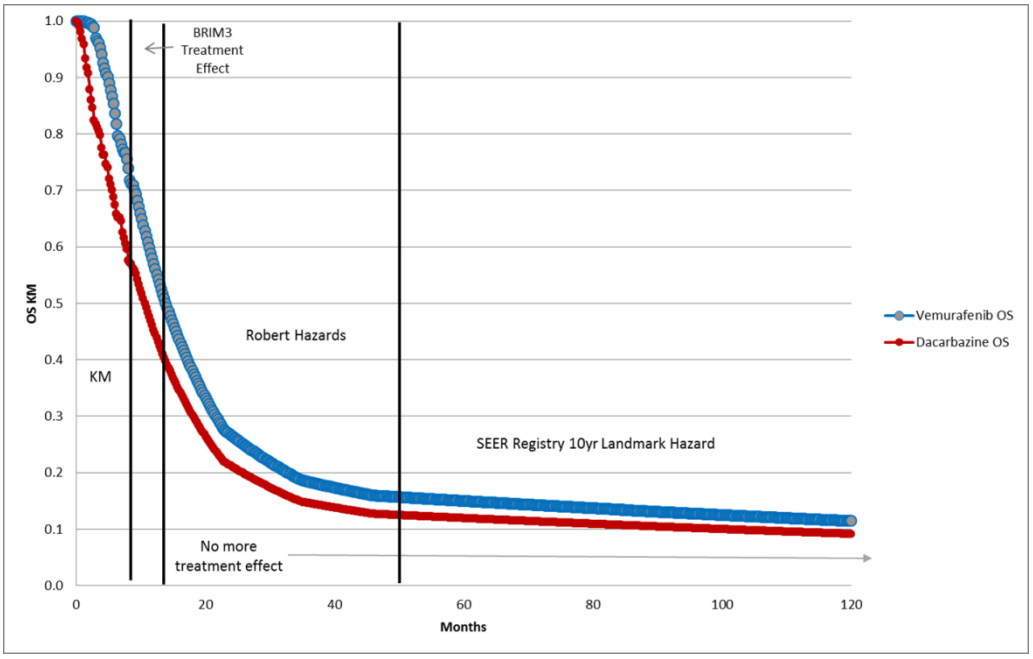
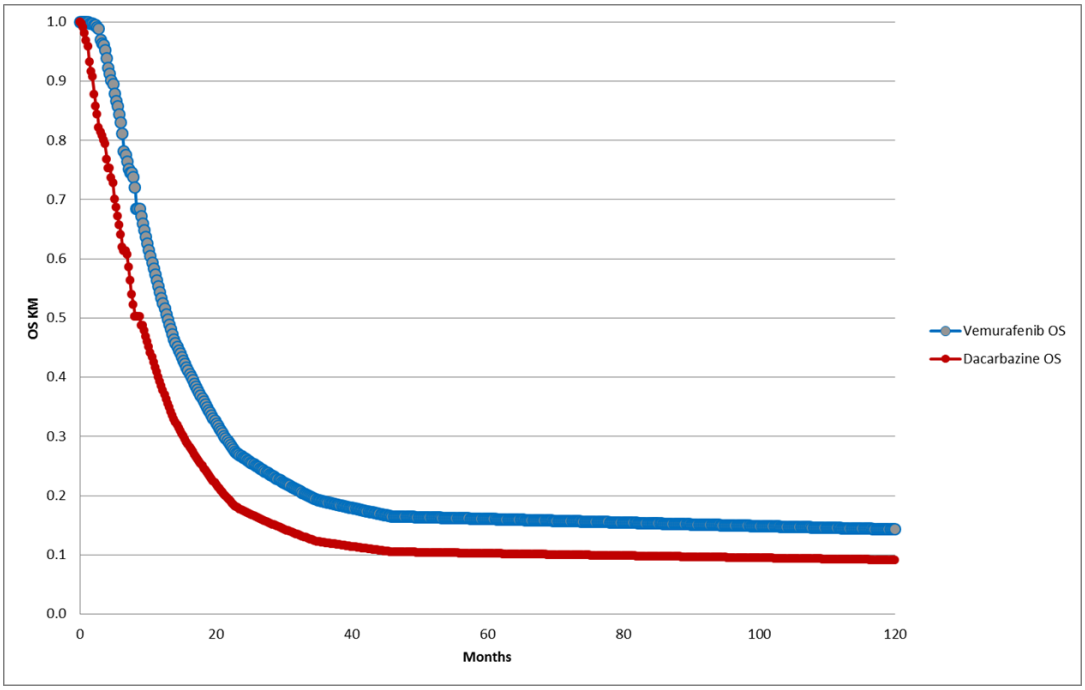


Figure 62: OS Scenario 3 – Base case with continued treatment effect until all patients no longer receiving vemurafenib (month 35)



It should be noted that range of alternative OS sensitivity analyses could have been conducted (using the Balch 10yr landmark figures, using the SEER or Balch data straight from BRIM3 rather than using the Robert data as a bridge, carrying on the hazards observed in BRIM3 to the x-axis, applying the longer term hazards in the vemurafenib arm later than in the dacarbazine etc), however solely the three presented above are included in the model. As the ICERs produced using the above extrapolations are all above the thresholds commonly employed in NICE appraisals (even in the case of the most optimistic scenario) the modelling of alternative extrapolation appears to add little to the decision faced.

The following utility value scenarios were also tested:

Table 43: Utility Sensitivity Analyses Conducted

Scenario	Description
1	Base-Case (Beusterien utilities used for all health states with weighting of response/stable disease values by BRIM3 response rates)
2	Base-Case with higher PD utility value used to reflect the potential for patients in 'tail' of survival curve to have lower tumour burden and therefore improved HRQoL (Beusterien utilities used for PFS with Hodi EORTC-QLQ-C30 mapped utility from ipilimumab appraisal used for PD)
3	Hodi EORTC-QLQ-C30 mapped values (Hodi mapped EORTC-QLQ-C30 values from ipilimumab appraisal used for all health states –no further disutility of AEs captured)
4	Hodi SF-36 mapped values (Hodi mapped SF-36 values from ipilimumab appraisal used for all health states –no further disutility of AEs captured)

6.5.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was conducted utilising the distributions detailed previously. The possibility of including a range of different potential long-term extrapolations within PSA (with the probability of each being used in a simulation defined by clinical expert opinion) was considered but dismissed as it was felt the uncertainty faced was so substantial the probability of each potential extrapolation occurring could not be reasonably estimated. Therefore this parameter was not varied in PSA. This will clearly result in the underestimation of the uncertainty associated with the modelling undertaken in the PSA results. However given the magnitude of the ICERs estimated in both the base-case modelling and deterministic sensitivity analyses this omission appears to have little impact upon decision uncertainty (i.e. deterministic analysis demonstrates the ICERs are high and very uncertain and so PSA adds little beyond these findings) .

6.6 Results

Clinical outcomes from the model

6.6.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 44: Model results compared with clinical data - Vemurafenib

Outcome	Clinical trial result	Model result
Progression-free survival (median)	6.2 months	6.2 months
Overall survival (median)	13.2 months (Oct) Not Reached (Mar)	12.9 months
Response Rate	48.4%	48.4%

Table 45: Model results compared with clinical data - Dacarbazine

Outcome	Clinical trial result	Model result
Progression-free survival (median)	1.6 months	1.6 months
Overall survival (median)	9.9 months (Oct) 8.8 months (Mar)	8.8 months
% patients alive at 10 years	9.1% (SEER registry)	9.1%
Response Rate	5.5%	5.5%

The two tables above show that the model perfectly predicts median PFS and response rates from BRIM3 (perhaps unsurprisingly given that response rates are taken straight from the study and applied in the model as an input and

because the PFS curves from BRIM3 were used directly in the model until beginning extrapolation (which began after the medians had been reached)).

The model also predicts the median OS for patients receiving dacarbazine extremely well (at least if comparing to the less confounded of the two cuts available – reasons for using the March rather than October cut have been stated previously in section 6.3.1. and so are not reiterated here).

The fact that the model does not predict the vemurafenib median OS precisely from the October cut is not unsurprising given that it is based upon the March cut. As shown when discussing OS extrapolation the stabilised hazard associated with death in the vemurafenib arm did drop marginally between the two cuts and so the slightly higher median in the later cut than the model predicts based upon the earlier cut is to be expected.

6.6.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The model runs for 30 years on a weekly cycle length (1,560 cycles).

Reproducing the Markov trace would require approximately 35 pages of the submission. As this submission is already 270 pages long this information is has not been reproduced within the template. The trace is available within the model and can be provided as a separate appendix document if required.

6.6.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

See response to 6.7.2 above.

6.6.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a

combination of other states, please present disaggregated results. For example:

Table 46: Model outputs by clinical outcomes – vemurafenib

Outcome	LY	QALY	Cost (£)
Progression-free survival	[redacted]	[redacted]	[redacted]
Post-progression survival	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]

LY, life years; QALY, quality-adjusted life year

Table 47: Model outputs by clinical outcomes – dacarbazine

Outcome	LY	QALY	Cost (£)
Progression-free survival	[redacted]	[redacted]	[redacted]
Post-progression survival	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]

LY, life years; QALY, quality-adjusted life year

6.6.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 48: Summary of QALY gain by health state

Health state	QALY (vemurafenib)	QALY (dacarbazine)	Increment	Absolute increment	% absolute increment

PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 49: Summary of costs by health state

Health state	Cost (vemurafenib)	Cost (dacarbazine)	Increment	Absolute increment	% absolute increment
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 50: Summary of predicted resource use by category of cost

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]
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Base-case analysis

6.6.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 51: Base-case results

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

Cost per life-year gained = £64,891

Sensitivity analyses

6.6.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Table 52: Parameters varied in deterministic sensitivity analysis

Parameter	Base-Case Value	Low Value	High Value		Base-Case ICER	Low Value ICER	High Value ICER
Transition Probabilities							
Monthly hazard of disease progression after month 9 (vemurafenib) – note: KM used before this point in time.	0.2087	-10%	+10%		£94,267	£95,486	£93,258
Monthly hazard of disease progression after month 7 (dacarbazine) - note: KM used before this point in time.	0.2437	-10%	+10%		£94,267	£94,352	£94,197
Monthly hazard of death between month 9 and month 14 (vemurafenib). note: KM used	0.0761				£94,267	£87,279	£102,283

before this point in time.		-10%	+10%				
Monthly hazard of death between month 9 and month 14 (dacarbazine). note: KM used before this point in time.	0.0855	-10%	+10%		£94,267	£100,775	£88,808
Monthly hazard of death between month 14 and month 23 (both arms)	0.0658	-10%	+10%		£94,267	£90,977	£97,618

Monthly hazard of death between month 23 and month 35 (both arms)	0.0328	-10%	+10%		£94,267	£92,290	£96,258
Monthly hazard of death between month 35 and month 46 (both arms)	0.0141	-10%	+10%		£94,267	£93,545	£94,990
Monthly hazard of death from month 46 onwards - note: model includes IF statement linked to age/gender adjusted background mortality so that highest rate of this figure and background mortality is used in model	0.001905	-50%	+50%		£94,267	£90,539	£98,629

Utility Values						
Progression Free Survival (Response)	0.85	0.833 (Lower confidence interval)	0.867 (Upper confidence interval)	£94,267	£95,037	£94,283
Progression Free Survival (Stable Disease)	0.77	0.755 (Lower confidence interval)	0.785 (Upper confidence interval)	£94,267	£93,401	£94,271
Progressed Disease	0.59	0.578 (Lower confidence interval)	0.602 (Upper confidence interval)	£94,267	£95,302	£94,289
Skin reaction (Rash)	-0.03	-0.0297 (Lower confidence interval)	-0.0303 (Upper confidence interval)	£94,267	£94,264	£94,268

Neutropenia	-0.08973	-0.0088, (Lower confidence interval)	-0.091 (Upper confidence interval)	£94,267	£94,271	£94,266
Resultant PFS Values	PFS vem = 0.806 PFS dac = 0.767	Dac PFS utility (0.767) applied to both treatments	Vem PFS utility (0.806) applied to both treatments	£94,267	£98,339	£96,070
Costs						
Pharmacy costs when vemurafenib dispensed	£13	£6.63 (Lower confidence interval if standard error = 1/4 base	£19.37 (Upper confidence interval if standard	£94,267	£94,174	£94,360

		case value (assumption))	error = 1/4 base case value (assumption))				

Dacarbazine Pharmacy Cost	£13	£6.63 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£19.37 (Upper confidence interval if standard error = 1/4 base case value (assumption))	£94,267	£94,325	£94,208
Dacarbazine Administration Cost	£248	£126.48 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£369.52 (Upper confidence interval if standard error = 1/4 base case value (assumption))	£94,267	£95,385	£93,149
		£192.78	£563.22		£92,990	£95,544

Monthly PFS BSC Cost	£378	(Lower confidence interval if standard error = 1/4 base case value (assumption))	(Upper confidence interval if standard error = 1/4 base case value (assumption))	£94,267		
Monthly PD BSC Cost	£378	£192.78 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£563.22 (Upper confidence interval if standard error = 1/4 base case value (assumption))	£94,267	£92,313	£96,221
Terminal Care Cost	£5,401	£2,754.51 (Lower confidence interval if	£8,047.49 (Upper confidence interval if	£94,267	£94,379	£94,155

		standard error = 1/4 base case value (assumption))	standard error = 1/4 base case value (assumption))				
Cost of Rash	£126.96	£64.75 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£189.17 (Upper confidence interval if standard error = 1/4 base case value (assumption))		£94,267	£94,258	£94,276
Cost of Neutropenia	£407.38	£207.76 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£607.00 (Upper confidence interval if standard error = 1/4 base case value (assumption))		£94,267	£94,296	£94,281

Cost of cuSCC/ keratocanthoma	£115	£58.65 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£171.35 (Upper confidence interval if standard error = 1/4 base case value (assumption))	£94,267	£94,253	£94,281
Patient Characteristics						
Age	54	45	65	£94,267	£93,071	£94,584
BRAF mutation incidence	48%	40%	60%	£94,267	£94,405	£94,129
General Parameters						
Time Horizon	30 years	20 years	-	£94,267	£103,793	-
Costs	3.5%	0%	6%	£94,267	£98,346	£92,178

Discount Rate						
Health Outcomes Discount Rate	3.5%	0%	6%	£94,267	£70,358	£110,535
Both Discount Rates	3.5%	0%	6%	£94,267	£73,397	£108,090

Figure 63: Deterministic Sensitivity Analysis Tornado Diagram

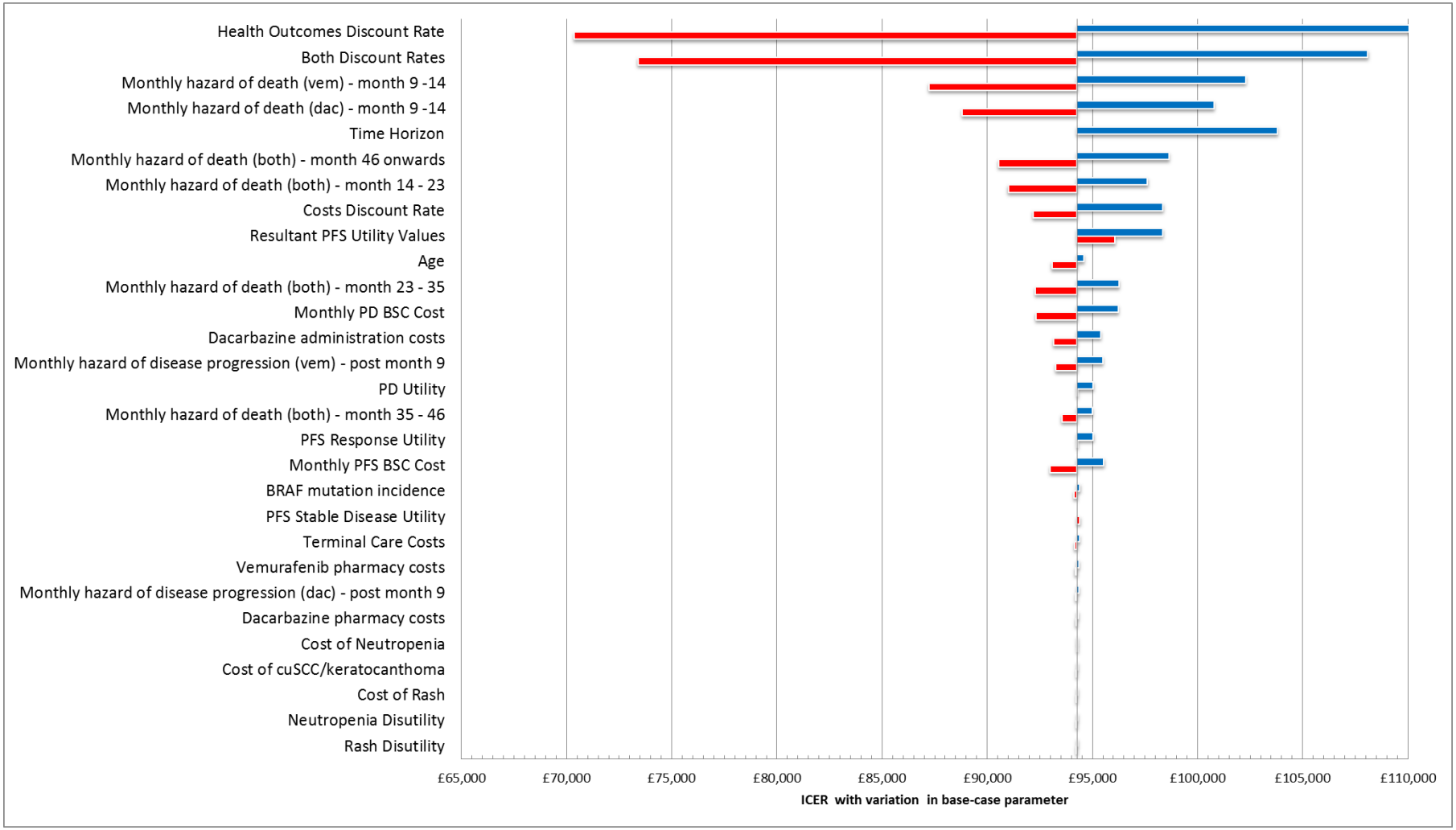

Health Outcomes Discount Rate
Both Discount Rates
Monthly hazard of death (vem) - month 9 -14
Monthly hazard of death (dac) - month 9 -14
Time Horizon
Monthly hazard of death (both) - month 46 onwards
Monthly hazard of death (both) - month 14 - 23
Costs Discount Rate
Resultant PFS Utility Values
Age
Monthly hazard of death (both) - month 23 - 35
Monthly PD BSC Cost
Dacarbazine administration costs
Monthly hazard of disease progression (vem) - post month 9
PD Utility
Monthly hazard of death (both) - month 35 - 46
PFS Response Utility
Monthly PFS BSC Cost
BRAF mutation incidence
PFS Stable Disease Utility
Terminal Care Costs
Vemurafenib pharmacy costs
Monthly hazard of disease progression (dac) - post month 9
Dacarbazine pharmacy costs
Cost of Neutropenia
Cost of cuSCC/keratocanthoma
Cost of Rash
Neutropenia Disutility
Rash Disutility
£65,000
£70,000
£75,000
£80,000
£85,000
£90,000
£95,000
£100,000
£105,000
£110,000
ICER with variation in base-case parameter

Table 53: OS Sensitivity Analyses Results

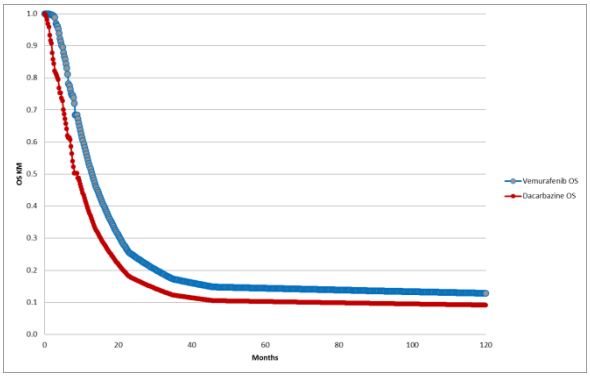
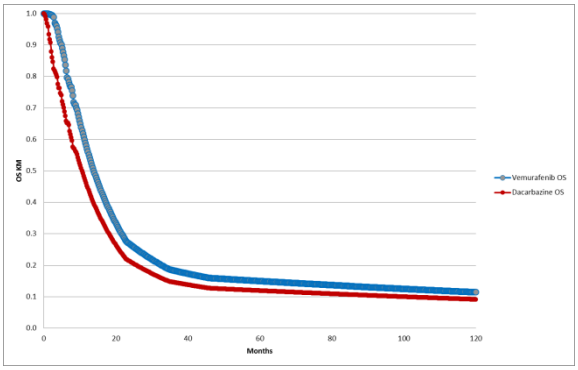
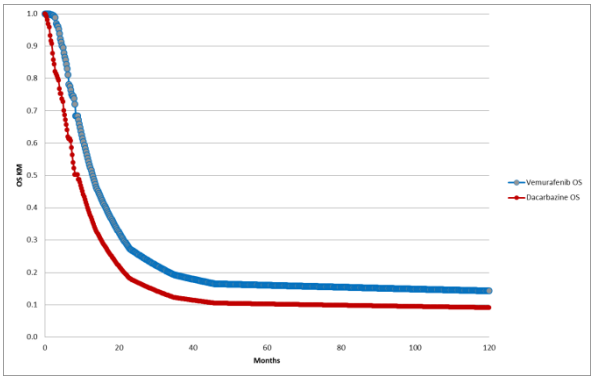
Scenario	Description	OS Curve	ICER
1	Base-Case		£94,267
2	October Cut		£128,060
3	Base-Case with 34 month treatment effect		£77,343

Table 54: Utility Sensitivity Analyses Conducted

Scenario	Description	ICER
1	Base-Case	£94,267
2	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
3	Hodi EORTC-QLQ-C30 mapped values	£83,643
4	Hodi SF-36 mapped values	£103,345

If OS sensitivity analysis 3 (the most optimistic extrapolation tested) is combined with utility sensitivity analysis 2 (the use of the Beusterien PFS utility values with the Hodi EORTC-QLQ-C30 PD utility value) the ICER is £65,747. If this analysis is combined with the setting of the discount rate for health outcomes to 0% an ICER of £46,524 is estimated.

6.6.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

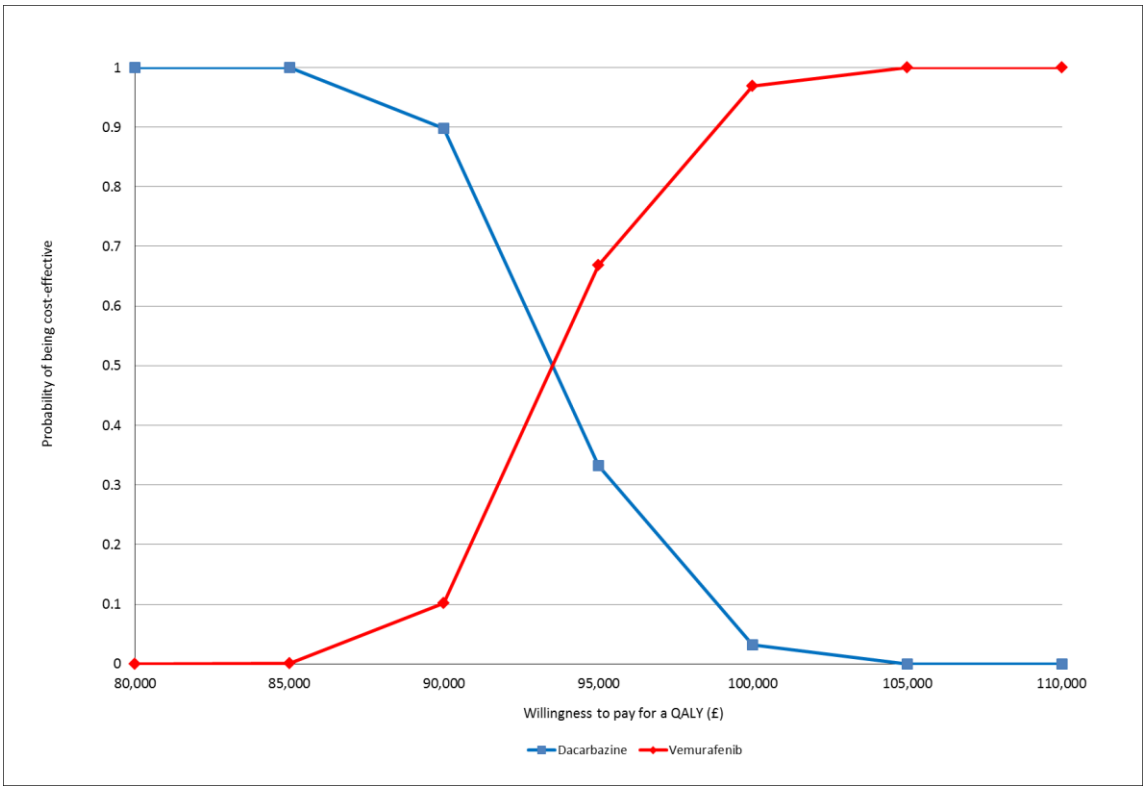
Whilst PSA was conducted it should be noted that the parameter subject to the most uncertainty (overall survival) was not varied probabilistically as there appears to be no reasonable way of defining which potential extrapolations should be given a higher likelihood of occurring than any other.

Due to this omission the PSA therefore significantly understates the uncertainty associated with the incremental QALY gain provided by vemurafenib.

Results

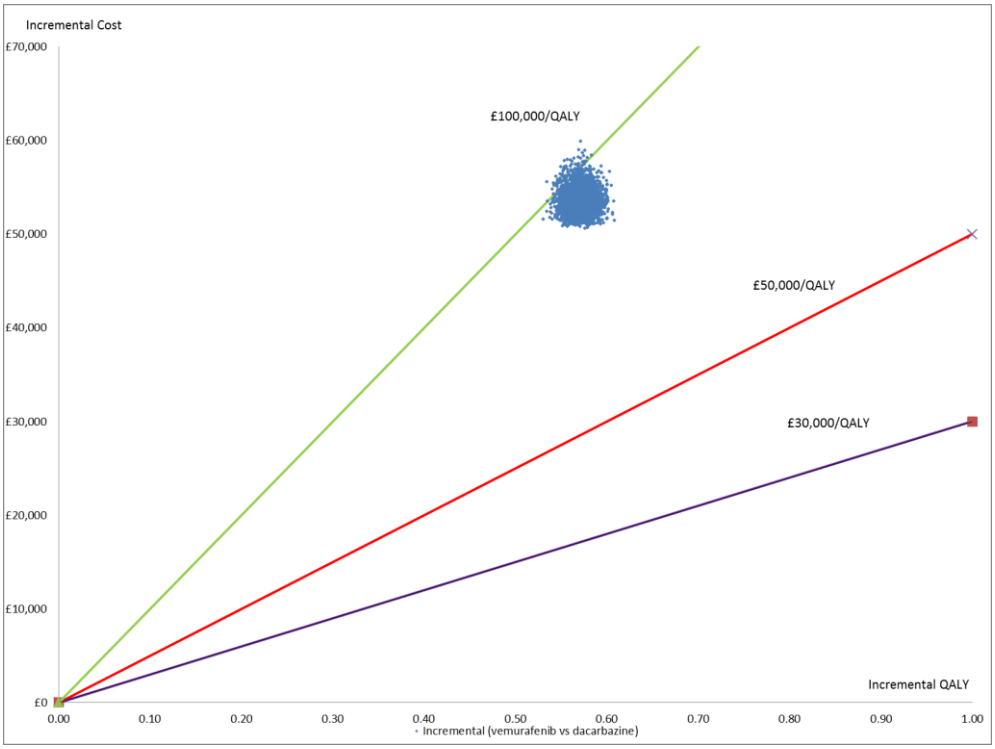
In the 3,000 simulations conducted vemurafenib would be considered as cost-effective in 0% of simulations up to a value of £85,000/QALY gained.

Figure 64: Cost Effectiveness Acceptability Curves



At a threshold of £95,000/QALY gained vemurafenib would be considered as being cost-effective in 66.8% simulations with that figure rising to 96.9% of simulations at a threshold of £100,000/QALY gained.

Figure 65: Cost Effectiveness Scatterplot



6.6.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

All of the sensitivity analyses conducted are detailed above.

6.6.10 What were the main findings of each of the sensitivity analyses?

In all sensitivity analyses conducted the ICER associated with vemurafenib remained above the levels typically considered acceptable.

The ICER is most sensitive to the long term projection of overall survival employed and to the post-progression utility values used. In comparison to these two parameters the influence of other parameters subject to uncertainty is relatively minor.

There is relatively high certainty around the incremental cost of vemurafenib (driven largely by drug costs) which when compared to a highly uncertain level of incremental QALY benefit results in ICERs which are relatively high and similarly subject to high level of uncertainty.

6.6.11 What are the key drivers of the cost-effectiveness results?

The key drivers of the model are the cost of vemurafenib, the long term survival projection employed and the post-progression utility values used.

6.7 Validation

6.7.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model was validated by a health economist not involved in the development of the submission. This health economist checked the models functionality and noted only minor errors which have since been corrected (i.e.

the AE costs associated with dacarbazine had been double counted in a previous draft of the model).

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.

6.8 Subgroup analysis

No subgroup analysis was conducted.

6.9 Interpretation of economic evidence

6.9.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is no published literature on the cost-effectiveness of vemurafenib.

6.9.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

The evaluation is founded upon the BRIM3 RCT and so should be representative of all patients who fit within the BRIM3 inclusion criteria.

6.9.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Weaknesses

1. The model is heavily reliant upon long-term projection of overall survival due to the immaturity of the BRIM3 data.

2. The data available to inform this long-term projection is limited to a general melanoma population and the influence of BRAF mutations upon survival outcomes is currently uncertainty. There is no historical control data on the survival of patients with BRAF V600 mutated advanced melanoma untreated with vemurafenib and there is no data on the longer term treatment impact of vemurafenib upon survival.

3. There is no randomised controlled data with which to assess the cost-effectiveness of vemurafenib as a second or later line treatment.

Strengths

1. BRIM3 was a well conducted study conducted in patients broadly representative of patients expected to be treated in England/Wales

2. The model utilises a range of health state costs which have been used, and accepted, in the only other NICE appraisal in advanced melanoma

3. The cost of vemurafenib included in the model includes consideration of wastage

4. Whilst the precise ICER associated with vemurafenib is associated with significant uncertainty the level of decision uncertainty is relatively low as in all sensitivity analyses the ICER remains above the range typically considered acceptable.

6.9.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The key driver of the model is overall survival and so the incorporation of more mature data on either the baseline risk of death of BRAF mutated melanoma patients or the longer term treatment effect associated with vemurafenib would greatly improve the robustness of the model.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

As described in Section 2.2 there expected to be 847 patients eligible to receive vemurafenib per year. If we assume a population growth rate of 0.5% per annum and this results in the following yearly eligible populations:

Table 55: Eligible population by year

Year	1	2	3	4	5
Eligible Population	847	851	856	860	864

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

It is assumed that all patients currently receive dacarbazine as a first line treatment.

7.3 What assumption(s) were made about market share (when relevant)?

It was assumed that 30% of eligible patients in the year following NICE approval would receive vemurafenib with that figure rising to 55% in the fifth

year following approval. The market share figures used in years 2, 3 and 4 are presented in the table below.

Table 56: Market Share Assumptions

Year	1	2	3	4	5
% patients treated with vemurafenib	30%	35%	40%	45%	55%

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The budget impact calculations include all the additional costs of treatment with vemurafenib as included in the de novo economic model and discussed in Section 5.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The budget impact calculations are based upon the output of the economic model.

7.6 Were there any estimates of resource savings? If so, what were they?

No.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 57: Budget impact by year

Year	1	2	3	4	5
Budget Impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No.

8 References

Bedikian AY et al, Phase 3 study of docosahexaenoic acid–paclitaxel versus dacarbazine in patients with metastatic malignant melanoma. Annals of Oncology 22: 787–793, 2011

Beusterien KM et al, Societal Societal preference values for advanced melanoma health states in the United Kingdom and Australia.
British Journal of Cancer (2009) 101, 387–389

Brookmeyer R, Crowley JJ. A confidence interval for median survival time. Biometrics 1982;38:29−4

Clinical Study Report – NP22657: An Open-Label, Multi-Centre, Phase II Study of Continuous Oral Dosing of vemurafenib in Previously Treated Patients With Metastatic Melanoma. Report No. 1038633. April 2011

Clinical Study Report – NO25026 –BRIM 3: A Randomized, Open-label, Controlled, Multi-centre, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving vemurafenib or Dacarbazine. Research Report Number 1039652. April, 2011

Cormier JN et al. Prospective assessment of the reliability, validity, and sensitivity to change of the Functional Assessment of Cancer Therapy-Melanoma questionnaire. Cancer. 2008 May 15;112(10):2249-57

Bloom KJ et al. Molecular testing for BRAF V600 mutations in the BRIM-2 trial of the BRAF inhibitor vemurafenib in metastatic melanoma. ASCO 2011: J Clin Oncol 2011; 29: (15 supp) abstract 10523

CRD (2008). Guidance for Undertaking Reviews in Healthcare. http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf (last accessed on 10/10/2011)

Hoyle M, Crathorne L, Peters J, Jones-Hughes T, Cooper C, Napier M, Tappenden P, Hyde C. (2011). The effectiveness and cost effectiveness of cetuxmab (mono- or combination therapy, 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. University of Exeter (Report).

McArthur GA et al. Vemurafenib improves overall survival compared to dacarbazine in advanced BRAFV600E-mutated melanoma: Updated survival results from a Phase III randomised, open-label, multicentre trial (Abstract #28LBA). ECCO/ESMO 2011.

Millar et al. 'A service evaluation to compare secondary care resource use between XELOX and FOLFOX-6 regimens in the treatment of metastatic colorectal cancer from a UK National Health Service (NHS) perspective' Presented at ISPOR Athens. November 9th - 11th 2008.

Nafees et al. 'Health State Utilities for Non-Small Cell Lung Cancer' Health and Quality of Life Outcomes 2008, 6:84

NICE TA227: Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer (2011). http://guidance.nice.org.uk/TA227 (last accessed on 10/10/2011)

NICE: Ipilimumab for previously treated unresectable stage III or IV malignant melanoma (ongoing).http://guidance.nice.org.uk/TA/WaveCRS2/48 (last accessed on 30/01/2011)

PSSRU 'Unit Costs of Health and Social Care 2010' http://www.pssru.ac.uk/uc/uc2010contents.htm (last accessed on 10/10/2011)

Ribas A et al. BRIM2: An Open-label, Multi-centre Phase II Study of Vemurafenib (PLX4032, RG7204) in Previously Treated Patients with BRAFV600E Mutation-positive Metastatic Melanoma. ASCO 2011 (Abstract #8509)

Robert C et al. Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. NEJM. 364;26. 2012.

Sosman J et al. An open-label, multicenter phase II study of continuous oral dosing of RG7204 (PLX4032) in previously treated patients with BRAF V600E mutation positive metastatic melanoma.7th International Melanoma Congress, 2010.

Sosman JA et al. Long-term follow-up of BRAFV600mutated metastatic melanoma patients treated with vemurafenib reveals prolonged survival. NEJM. 2012 (in-press)

Xing Y et al. Conditional Survival Estimates Improve Ove rTime for Patients With Advanced Melanoma Cancer. May 1, 2010.

Zelboraf (vemurafenib) Summary of Product Characteristics RXUKZELB00029 (December 2011)

Appendices

8.1 Appendix 1

8.1.1 SPC/IFU, scientific discussion or drafts.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline - Datastar
- Embase - Datastar
- Medline (R) In-Process - Datastar
- The Cochrane Library at http://onlinelibrary.wiley.com/o/cochrane/
- ASCO at www.asco.org
- ECCO at http://annonc.oxfordjournals.org
- European Multidisciplinary Cancer Congress 2011 at http://stockholm2011.ecco-org.eu
- 8th and 9th International Symposium on Targeted Anticancer Therapies at http://annonc.oxfordjournals.org
- 7th International Melanoma Congress Sydney 2010 at www.melanoma2010.org

9.2.2 The date on which the search was conducted.

Medline, Embase and Medline in process were searched on the 15 December 2011. ASCO was also searched on 7 December 2011, and ECCO 2010 and the European Multidisciplinary Cancer Congress (ECCO 16, ESMO 36 and ESTRO 30) were searched on the 12 December 2011. The 8th and 9th International Symposium on Targeted Anticancer Therapies and the 7th International Melanoma Congress were also searched on the 7 December 2011. A free-text search of the Cochrane Library was conducted on the 12 December 2011.

9.2.3 The date span of the search.

The Dialog Datastar search used the database from 2003 to the present date; conference sites were searched as described in section 9.2.1.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Datastar was searched using the following strategy:

Search Strategy

No.	Database	Search term	Info added since	Results
1	EMYY	melanoma	unrestricted	69351
2	EMYY	MELANOMA.W..DE.	unrestricted	47805
3	EMYY	vemurafenib	unrestricted	161
4	EMYY	VEMURAFENIB.W..DE.	unrestricted	158
5	EMYY	Zelboraf	unrestricted	18
6	EMYY	RG7204	unrestricted	20
7	EMYY	PLX–4032.DE.	unrestricted	252
8	EMYY	3 OR 4 OR 5 OR 6 OR 7	unrestricted	412
9	EMYY	2 AND 8	unrestricted	327
10	EMYY	RCT OR randomised OR randomized	unrestricted	400370
11	EMYY	9 AND 10	unrestricted	30
12	EMYY	11 AND REVIEW=YES	unrestricted	18
13	EMYY	11 NOT 12	unrestricted	12
14	EMYY	ipilimumab	unrestricted	816
15	EMYY	IPILIMUMAB.W..DE.	unrestricted	798
16	EMYY	Yervoy	unrestricted	40
17	EMYY	MDX–010	unrestricted	197
18	EMYY	MDX–101	unrestricted	11
19	EMYY	14 OR 15 OR 16 OR 17 OR 18	unrestricted	820
20	EMYY	2 AND 19	unrestricted	563
21	EMYY	RCT OR randomised OR randomized	unrestricted	400370
22	EMYY	20 AND 21	unrestricted	75
23	EMYY	22 AND REVIEW=YES	unrestricted	35
24	EMYY	22 NOT 23	unrestricted	40
25	EMYY	dacarbazine	unrestricted	8850
26	EMYY	DACARBAZINE.W..DE.	unrestricted	8705
27	EMYY	DTIC	unrestricted	519
28	EMYY	imidazole ADJ carboxamide	unrestricted	62
29	EMYY	25 OR 26 OR 27 OR 28	unrestricted	8951
30	EMYY	2 AND 29	unrestricted	2649

31	EMYY	RCT OR randomised OR randomized	unrestricted	400370
32	EMYY	30 AND 31	unrestricted	320
33	EMYY	32 AND REVIEW=YES	unrestricted	137
34	EMYY	32 NOT 33	unrestricted	183
35	EMYY	13 OR 24 OR 34	unrestricted	211
36	MEYY	melanoma	unrestricted	55451
37	MEYY	vemurafenib	unrestricted	26
38	MEYY	MELANOMA.W..DE.	unrestricted	33861
39	MEYY	Zelboraf	unrestricted	3
40	MEYY	RG7204	unrestricted	16
41	MEYY	PLX4032	unrestricted	75
42	MEYY	37 OR 39 OR 40 OR 41	unrestricted	90
43	MEYY	38 AND 42	unrestricted	57
44	MEYY	RCT OR randomised OR randomized	unrestricted	407654
45	MEYY	43 AND 44	unrestricted	3
46	MEYY	ipilimumab	unrestricted	216
47	MEYY	Yervoy	unrestricted	7
48	MEYY	MDX-010	unrestricted	0
49	MEYY	MDX101	unrestricted	0
50	MEYY	MDX-101	unrestricted	0
51	MEYY	46 OR 47	unrestricted	216
52	MEYY	38 AND 51	unrestricted	116
53	MEYY	44 AND 52	unrestricted	20
54	MEYY	dacarbazine	unrestricted	3591
55	MEYY	dacarbazine	unrestricted	3591
56	MEYY	DACARBAZINE.W..DE.	unrestricted	3053
57	MEYY	DTIC	unrestricted	418
58	MEYY	imidazole ADJ carboxamide	unrestricted	65
59	MEYY	54 OR 56 OR 57 OR 58	unrestricted	3706
60	MEYY	38 AND 59	unrestricted	858
61	MEYY	44 AND 60	unrestricted	151
62	MEYY	61 AND REVIEW=YES	unrestricted	37
63	MEYY	61 NOT 62	unrestricted	114

64	MEYY	53 AND REVIEW=YES	unrestricted	9
65	MEYY	53 NOT 64	unrestricted	11
66	MEYY	45 AND REVIEW=YES	unrestricted	0
67	MEYY	45 OR 65 OR 63	unrestricted	124
68	MEIP	melanoma	unrestricted	1643
69	MEIP	vemurafenib	unrestricted	20
70	MEIP	Zelboraf	unrestricted	3
71	MEIP	RG7204	unrestricted	5
72	MEIP	PLX4032	unrestricted	10
73	MEIP	69 OR 70 OR 71 OR 72	unrestricted	27
74	MEIP	68 AND 73	unrestricted	24
75	MEIP	RCT OR randomised OR randomized	unrestricted	11032
76	MEIP	74 AND 75	unrestricted	0
77	MEIP	ipilimumab	unrestricted	47
78	MEIP	Yervoy	unrestricted	4
79	MEIP	MDX-010	unrestricted	0
80	MEIP	MDX-101	unrestricted	0
81	MEIP	77 OR 78	unrestricted	47
82	MEIP	68 AND 81	unrestricted	37
83	MEIP	75 AND 82	unrestricted	7
84	MEIP	83 AND REVIEW=YES	unrestricted	0
85	MEIP	dacarbazine	unrestricted	57
86	MEIP	DTIC	unrestricted	8
87	MEIP	imidazole ADJ carboxamide	unrestricted	0
88	MEIP	85 OR 86	unrestricted	59
89	MEIP	68 AND 88	unrestricted	35
90	MEIP	75 AND 89	unrestricted	3
91	MEIP	90 AND REVIEW=YES	unrestricted	0
92	MEIP	83 OR 90	unrestricted	9
93	EMYY MEIP MEYY	combined sets 35, 67, 92	unrestricted	344
94	EMYY MEIP MEYY	dropped duplicates from 93	unrestricted	100
95	EMYY MEIP MEYY	unique records from 93	unrestricted	244

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

No internal databases were used.

9.2.6 The inclusion and exclusion criteria.

See section 5.

9.2.7 The data abstraction strategy.

See the table above for the Medline, Embase and Medline-in-process search strategies.

ASCO was searched with a free-text search for ‘vemurafenib’ and ‘melanoma’, ‘RG7204’ and ‘melanoma’, ‘PLX4032’ and ‘melanoma’, and ‘Zelboraf’ and ‘melanoma’. The 8th and 9th International Symposium on Targeted Anticancer Therapies and the 7th International Melanoma Congress websites were searched with ‘BRAF’, vemurafenib, RG7204, and PLX4032 as search terms. The ESMO abstracts were searched on the Annals of Oncology site, with the terms BRAF, vemurafenib, RG7204, and PLX4032. The European Multidisciplinary Cancer Congress 2011 was searched online at http://stockholm2011.ecco-org.eu for the term vemurafenib.

8.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

8.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Table 58: Appendix 3 - Quality assessment of RCT (BRIM 3)

ClinicalTrials.gov Identifier: NCT01006980. **Roche trial no. NO25026** **(BRIM 3)**		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Yes. After archival tumour samples for each patient tested positive for the BRAFV600 mutation using the cobas® 4800 BRAF V600 Mutation Test and all other eligibility criteria were met, patients were randomly assigned in a 1:1 ratio to open-label treatment with either vemurafenib or dacarbazine. The randomization was designed to minimize imbalances between treatment groups within the 4 stratification factors (stratified according to American Joint Committee on Cancer stage (IIIC, M1a, M1b, or M1c), ECOG performance status (0 or 1), geographic region (North America, Western Europe, Australia or New Zealand, or other region), and serum lactate dehydrogenase level (normal or elevated)). Patients randomized into the study were not replaced. A centre could be replaced because of excessively slow recruitment or poor protocol adherence.	yes
Was the concealment of treatment allocation adequate?	This was an open-label study	n/a
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes – see Table 8	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was an open-label study	n/a
Were there any unexpected imbalances in	No	n/a

drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	n/a
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. This was the primary analysis. The co-primary endpoint for this study was progression-free survival (PFS), defined as time from randomization to disease progression or death due to any cause. The analysis population for PFS consisted of all ITT patients randomized by October 27, 2010 (at least 9 weeks prior to the clinical cut-off date of December 30, 2010). The 9-week interval was chosen to allow time for patients to have had their first scheduled post-baseline tumour assessment CT scan (per protocol at 6 weeks, +/- 7 days). The final analysis of PFS was performed as planned at the time of the interim analysis of OS in January 2011. The Type 1 error for the PFS endpoint was controlled at alpha = 0.005 (two-sided), as pre-specified in the SAP. Subsequent to the January 2011 DSMB meeting, data collection and cleaning were concluded for the purpose of this CSR. The clinical cut-off date for the analyses of PFS is the same as the clinical cut-off date for the analysis of OS (December 30, 2010). The analyses of	

	PFS are based on the final database for the CSR as described in Section 5.2.1.2. In the final database for this CSR, a total of 549 ITT patients (275 in the vemurafenib group and 274 in the dacarbazine group) were randomized at least 9 weeks prior to the clinical cut-off date of December 30, 2010 and were therefore evaluable for the analysis of PFS. Among the 549 ITT patients evaluable for analysis of PFS, a total of 286 patients had experienced disease progression or had died: 104 in the vemurafenib group and 182 in the dacarbazine group. The DSMB for Study NO25026 recommended release of the results of this study due to compelling efficacy based on review of results presented January 14, 2011 at the time of the planned interim analysis of OS. At that meeting, the DSMB determined that the pvalue from the log-rank test for OS ($p<0.0001$) crossed the efficacy boundary in favor of vemurafenib. The boundary had been determined so that the Type 1 error for the OS endpoint was controlled at alpha = 0.045 (two-sided), as pre-specified in the SAP. Therefore, the January 2011 interim	

	analysis of OS established that the results for OS were statistically significant in favour of vemurafenib. The SAP specified that 100% information was defined as 196 deaths. The interim analysis was planned to occur when approximately 50% information was available. Results in the DSMB report (after analysis involving 671 patients) showed that a total of 115 deaths (59% information) had occurred: 43 deaths in the vemurafenib group and 72 deaths in the dacarbazine group. Duration of survival was statistically significantly longer in the vemurafenib group than in the dacarbazine group ($p<0.0001$). The hazard ratio for death was 0.38 (95% CI: 0.26, 0.55), representing a 62.4% reduction in the hazard of death for patients in the vemurafenib group compared to patients in the dacarbazine group.	
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

8.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

N/A.

8.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

N/A.

8.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

The following information should be provided.

8.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

    - Medline – searched using the Proquest Dialog Datastar platform, which now incorporates Medline in Process into the Medline database

    - Embase – Proquest Dialog Datastar

    - Embase alerts - Proquest Dialog Datastar

    - The Cochrane Library at http://onlinelibrary.wiley.com/o/cochrane/

    - ASCO at www.asco.org

    - ECCO at http://annonc.oxfordjournals.org

- European Multidisciplinary Cancer Congress 2011 at http://stockholm2011.ecco-org.eu
- 8th and 9th International Symposium on Targeted Anticancer Therapies at http://annonc.oxfordjournals.org
- 7th International Melanoma Congress Sydney 2010 at www.melanoma2010.org

8.6.2 The date on which the search was conducted.

Medline and Embase/Embase alerts were searched on the 25 January 2012. ASCO was also searched on 7 December 2011, and ECCO 2010 and the European Multidisciplinary Cancer Congress (ECCO 16, ESMO 36 and ESTRO 30) were searched on the 12 December 2011. The 8th and 9th International Symposium on Targeted Anticancer Therapies, and the 7th International Melanoma Congress were also searched on the 7 December 2011. A free-text search of the Cochrane Library was conducted on the 12 December 2011.

8.6.3 The date span of the search.

Medline was not limited to a date span and hence covered from 1950 to the present date; Embase was searched from 1947 to the search date. Conference sites were searched as described in section 9.4.1.

8.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Proquest Dialog Datastar was searched using the following search strategy:

Set #	Search
S1	"vemurafenib" or "PLX4032" or "RG7204"
S2	EMB.EXACT.EXPLODE("melanoma") OR MESH.EXACT.EXPLODE("Melanoma")
S3	MESH.EXACT.EXPLODE("Randomized Controlled Trial") OR EMB.EXACT.EXPLODE("randomized controlled trial")
S4	S1 and S2
S5	(S4 NOT S3) NOT at.exact("Review" OR "Editorial")

ASCO was searched with a free-text search for ‘vemurafenib’ and ‘melanoma’, ‘RG7204’ and ‘melanoma’, ‘PLX4032’ and ‘melanoma’, and ‘Zelboraf’ and ‘melanoma’. The 8th and 9th International Symposium on Targeted Anticancer Therapies and the 7th International Melanoma Congress websites were searched with ‘BRAF’, vemurafenib, RG7204, and PLX4032 as search terms. The ESMO abstracts were searched on the Annals of Oncology site, with the terms BRAF, vemurafenib, RG7204, and PLX4032. The European Multidisciplinary Cancer Congress 2011 was searched online at http://stockholm2011.ecco-org.eu for the term vemurafenib.

8.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No other searches were conducted.

8.6.6 The inclusion and exclusion criteria.

Please see section 5.

8.6.7 The data abstraction strategy.

Please see section 5.

8.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

8.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Table 59: Appendix 3 - Quality assessment of RCT (BRIM 3)

ClinicalTrials.gov Identifier: NCT00949702 **Roche trial no. NP22657 (BRIM-2)**		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	This was a single arm open-label study	n/a
Was the concealment of treatment allocation adequate?	This was a single arm open-label study	n/a
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	This was a single arm open-label study	n/a
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was a single arm open-label study	n/a
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	This was a single arm open-label study	n/a
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	n/a
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. **Analysis population** The intent-to-treat (ITT) population was defined as all enrolled patients who receive at least one or a partial dose of vemurafenib. Efficacy analysis was based primarily on this population.	Yes

	Per-protocol (PP) population is a subpopulation of the ITT patients, excluding those patients with major protocol violations of inclusion/exclusion criteria and those with other violations affecting the efficacy assessments. Safety Population was defined as all patients who received at least one or a partial dose of study therapy will be included in the safety population. In this study, the ITT population is defined as the same as the safety population. BRAF V600E-Positive Population included ITT patients whose mutation status is confirmed by Sanger sequencing as V600E-positive, excluding other V600 mutations such as V600K, V600D, and V600R (defining the BRAF Non-V600E Mutations Population). Best overall response rate (BORR) and duration of response will be summarized for this population to assess treatment effects in the patients with confirmed V600E mutations. **Primary Efficacy Analysis** For the primary analysis, the BORR by IRC assessment, an estimate of the BORR and its 95% CI was determined and the 95% CI was constructed using	

	the Copper-Pearson method. In addition to the BORR analysis, BOR was summarized by the four RECIST 1.1 categories: CR, PR, SD, and PD as described in Section 2.5.2.2. The summary also includes a category for unevaluable (UE) patients, as assessed by the IRC. The BORR by IRC assessment was also summarized with the associated exact 95% (2-sided) CI using the Copper-Pearson method in the PP population. **Secondary Efficacy Analyses** Response assessments were compared between the IRC and investigators. Concordance in response assessments was reported as the agreement in numbers and percentages of responders (BOR of CR or PR) and non-responders, as assessed by both the IRC and investigators. Discordance in response assessments was reported as the numbers and percentages of patients whose BOR assessments were different between the IRC and investigators. When one of these assessments was missing it was considered a discordance. BORR by the investigator was summarized along with the associated exact 95% (two-sided) CI using the Copper-Pearson method. Duration of response by IRC, PFS by IRC, and OS were estimated using the Kaplan-Meier method, and the 95% CI for median	

	time was calculated using the Brookmeyer and Crowley method. The primary analysis of the study was performed when all treated patients have been followed up for at least 6 months after the last enrolled patient received the first dose of study medication.	
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

8.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

N/A. No specific search was conducted for adverse events associated with vemurafenib as due to the stage of development there is no routine use outside of clinical trials.

8.9 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

8.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

ProQuest was searched for databases Medline, Embase and Embase Alert. Note Medline-In-Process is now nested within Medline in the new ProQuest. EconLIT was searched via the American Economic Association (AEA) website

and NHS EED was searched using the University of York's 'Centre for Reviews and Dissemination' (CRD) website, both accessed on 17th January 2012.

8.9.2 The date on which the search was conducted.

17th January 2012.

8.9.3 The date span of the search.

9th December 2010 to 17th January 2012.

8.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

All 5 databases were searched with the following terms:

COST ADJ EFFECTIVENESS ADJ ANALYSIS OR COST ADJ UTILITY ADJ ANALYSIS OR COST ADJ BENEFIT ADJ ANALYSIS OR ECONOMIC ADJ MODEL OR DE ADJ NOVO ADJ MODELLING OR COST ADJ MINIMI?ATION ADJ ANALYSIS)

AND Melanoma

AND Metastatic OR Advanced

AND ENGLAND OR WALES OR UNITED ADJ KINGDOM OR UK

Zero results were found.

8.9.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

8.10 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

N/A.

8.11 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

8.11.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

ProQuest was searched for databases Medline, Embase and Embase Alert. Note Medline-In-Process is now nested within Medline in the new ProQuest. EconLIT was searched via the American Economic Association (AEA) website and NHS EED was searched using the University of York's 'Centre for Reviews and Dissemination' (CRD) website, both accessed on 17th January 2012.

8.11.2 The date on which the search was conducted.

17th January 2012.

8.11.3 The date span of the search.

9th December 2010 to 17th January 2012.

8.11.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 60: Search results from ProQuest - Utility

Set#	Searched for	Databases	Results
S1	(HEALTH ADJ RELATED ADJ QUALITY ADJ OF ADJ LIFE OR QUALITY ADJ ADJUSTED ADJ LIFE ADJ YEAR OR QALY[*2] OR SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL OR UTILITY ADJ VALUES OR UTILITY ADJ SCORE OR TTO OR TIME ADJ TRADE ADJ OFF OR SG OR STANDARD ADJ GAMBLE) AND la.exact("ENG")	Embase®,Embase® Alert,MEDLINE®	16046
S2	Melanoma AND la.exact("ENG")	Embase®,Embase® Alert,MEDLINE®	12708
S3	(Metastatic OR Advanced) AND la.exact("ENG")	Embase®,Embase® Alert,MEDLINE®	76307
S4	(S1 AND S2 AND S3) AND la.exact("ENG")	Embase®,Embase® Alert,MEDLINE®	11

NSH EED was searched using the terms:

(Quality adjusted life year or QALY or Qalies or EQ-5D or EQ-5D-5L or Euroqol or Time trade off or Standard Gamble or Utility value or Utility Score) AND (Melanoma) AND (Advanced or Metastatic) AND (Utility):TI

Zero results were found.

EconLIT was searched using:

(Quality adjusted life year or QALY or Qalies or EQ-5D or EQ-5D-5L or Euroqol or Time trade off or Standard Gamble or Utility value or Utility Score) AND (Melanoma) AND (Advanced or Metastatic) AND (Utility)

Zero results were found.

8.11.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No further searches were performed.

8.11.6 The inclusion and exclusion criteria.

Table 61: Exclusion criteria for utility studies

Is the paper in English?	No – Exclude
Does the abstract mention one or more utility terms (Quality of Life, HRQoL, Utility Values, or Utility Scores)	No – Exclude
Is the disease area metastatic or advanced melanoma?	No – Exclude
Is the paper a literature review of existing utility scores used in metastatic melanoma?	Yes – Exclude
Once a record has made it to here, it is retrieved and read in entirety and assessed against the following criteria:	
Does it derive utility values directly?	No – Exclude
Are utility values derived from the perspective of the general public?	No – Exclude
Are Time Trade Off or Standard Gamble methods of elicitation used to derive utility scores?	No – Exclude
Are utilities derived appropriate for modelling metastatic oncology health states such as PFS and PD?	No – Exclude

8.11.7 The data abstraction strategy.

Two individuals extracted articles as per the inclusion and exclusion criteria above. All search terms and inclusion and exclusion criteria were agreed upon before the search was conducted. After independently going through the articles, any disputes over including or excluding articles were discussed and reconciled by the two reviewers. All articles that could not be excluded were included in the review of relevant articles to help inform the economic model.

8.12 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

8.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

ProQuest was searched for databases Medline, Embase and Embase Alert. Note Medline-In-Process is now nested within Medline in the new ProQuest. EconLIT was searched via the American Economic Association (AEA) website and NHS EED was searched using the University of York's 'Centre for Reviews and Dissemination' (CRD) website, both accessed on 17th January 2012.

8.12.2 The date on which the search was conducted.

17th January 2012.

8.12.3 The date span of the search.

9th December 2010 to 17th January 2012.

8.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 62: Search results from ProQuest - Costs

Set#	Searched for	Databases	Results
S1	(SOCIOECONOMICS OR COST ADJ BENEFIT ADJ ANALYSIS OR COST ADJ EFFECTIVENESS ADJ ANALYSIS OR COST ADJ OF ADJ ILLNESS OR COST ADJ CONTROL OR ECONOMIC ADJ ASPECT OR FINANCIAL ADJ MANAGEMENT OR HEALTH ADJ CARE ADJ COST OR HEALTH ADJ CARE ADJ FINANCING OR HEALTH ADJ ECONOMICS ADJ HOSPITAL ADJ COST OR FISCAL OR FINANCIAL OR FINANCE OR FUNDING OR COST ADJ MINIMIZATION ADJ ANALYSIS OR COST ADJ ESTIMATE OR COST ADJ VARIABLE OR UNIT ADJ COST OR RESOURCE ADJ UTILISATION OR NHS ADJ COSTS) AND la.exact("ENG")	Embase®,Embase® Alert,MEDLINE®	21732
S2	Melanoma AND la.exact("ENG")	Embase®,Embase® Alert,MEDLINE®	12708
S3	(Metastatic OR Advanced) AND la.exact("ENG")	Embase®,Embase® Alert,MEDLINE®	76307
S4	(ENGLAND OR WALES OR UNITED ADJ KINGDOM OR UK) AND la.exact("ENG")	Embase®,Embase® Alert,MEDLINE®	345202
S5	(S1 AND S2 AND S3 AND S4) AND la.exact("ENG")	Embase®,Embase® Alert,MEDLINE®	3

NHS EED and EconLIT were searched using the following:

(Resource utilisation or NHS reference costs or Cost analysis) AND (Melanoma) AND (Advanced or Metastatic) AND (UK or England or Wales)

Zero results were found.

8.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No further searches were performed.

8.12.6 The inclusion and exclusion criteria.

Table 63: Exclusion criteria for cost studies

Is the paper in English?	No – Exclude
Does the abstract mention one or more cost terms (Costs, Resources, Economics)?	No – Exclude
Do costs mentioned apply to the United Kingdom?	No – Exclude
Is the disease area metastatic or advanced melanoma?	No – Exclude
Is the paper a literature review of existing costs used in metastatic melanoma?	Yes - Exclude
Once a record has made it to here, it is retrieved and read in entirety and included if the final exclusion 2 exclusions do not apply:	
Are costs derived directly from a large scale study (>100)?	No – Exclude
Is the study less than 5 years old?	No – Exclude

8.12.7 The data abstraction strategy.

Two individuals extracted articles as per the inclusion and exclusion criteria above. All search terms and inclusion and exclusion criteria were agreed upon before the search was conducted. After independently going through the articles, any disputes over including or excluding articles were discussed and reconciled by the two reviewers. All articles that could not be excluded were included in the review of relevant articles to help inform the economic model.

9 Related procedures for evidence submission

9.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

9.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to

provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential

information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

9.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the

evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).