NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Melanoma (unresectable/metastatic $BRAF^{V600}$ mutation-positive) - dabrafenib

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GlaxoSmithKline UK

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Executive summary

Background

The incidence of melanoma is increasing worldwide. In the UK, there are about 12,800 new melanoma diagnoses each year and in 2010, 2,203 people died from the disease. An activating mutation of the BRAF* protein in the mitogen-activated protein kinase (MAPK) pathway, which plays a critical role in regulating normal cell growth, differentiation and survival, has been identified as driving the development of approximately 50% of melanomas.

Dabrafenib – the technology

Dabrafenib (Tafinlar®) is a reversible, ATP-competitive inhibitor that selectively inhibits $BRAF^{V600}$ kinase activity.

Dabrafenib was granted a marketing authorisation by the European Medicines Agency (EMA) on 26th August 2013, and made commercially available in the UK on 1st January 2014. Dabrafenib is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation.

Dabrafenib is an oral therapy, available as 50mg and 75mg hard capsules. The recommended starting dose for dabrafenib is 150mg (two x 75mg capsules) twice daily; a total maximum daily dose of 300mg. Dabrafenib is taken continuously until the patient no longer derives benefit or develops unacceptable toxicity. Management of adverse reactions may require dose reduction or treatment interruption or discontinuation according to its adverse event profile. The list price of dabrafenib monotherapy is £1,400 per 28 x 75mg pack and £933.33 per 28 x 50mg pack.

Confirmation of $BRAF^{V600}$ mutation status using a validated test is required to select patients for treatment with dabrafenib. Due to UK-wide availability of vemurafenib, an alternative BRAF inhibitor, BRAF testing facilities are now part of routine management for patients with advanced/metastatic melanoma.

Comparators

The current standard of care for patients with $BRAF^{V600}$ mutation-positive metastatic melanoma is vemurafenib, which was licensed in February 2012 and recommended by NICE in December 2012, largely replacing dacarbazine. It is estimated that 92% of eligible patients in the UK are currently receiving vemurafenib, therefore this treatment is considered the main comparator for this appraisal. Dacarbazine was specified as a comparator in the scope for this appraisal and forms the comparator arm of the phase III trial for dabrafenib. Although dacarbazine is not expected to be widely used in this setting, results versus dacarbazine are presented as they allow comparisons with the appraisal of vemurafenib.

Clinical efficacy

A systematic review was undertaken to identify clinical evidence for dabrafenib and its comparators (vemurafenib and dacarbazine) as first-line treatments for patients with $BRAF^{V600}$ mutation-positive metastatic melanoma. BREAK-3, which compared dabrafenib versus dacarbazine provides the main evidence for dabrafenib. BRIM-3, which compared vemurafenib monotherapy versus dacarbazine was incorporated into indirect treatment comparisons (ITCs) with dabrafenib to allow comparisons between dabrafenib and vemurafenib.

* BRAF: serine/threonine-protein kinase B-Raf

In BREAK-3, a high proportion of patients crossed over upon progression from the control arm to receive dabrafenib. It is likely, therefore, that the true treatment impact of dabrafenib on overall survival (OS) was under-estimated. Statistical methods to adjust for this confounding were applied and the Rank Preserving Structural Failure Time Model (RPSFT) was deemed the most robust approach for this dataset.

Key outcomes for dabrafenib are summarised in Table 1 below.

Table 1. Key outcomes from BREAK 3 (ITT population)

		Dabrafenib monotherapy (BREAK-3 - BRF113683); NCT01227889 Latest PFS cut-off; 25 Jun 2012 OS update; 18 Dec 2012	
		Dabrafenib 150mb b.d. (N=187)	**Dacarbazine 1000mg/m^2 (N = 63)**
Primary outcome(s) & measures	**PFS; months Median (95% CI)**	6.9 (5.2, 9.0)	2.7 (1.5, 3.2)
	HR (95% CI); p-value	0.37 (0.24, 0.58); p<0.0001	
Secondary outcome(s) & measures	**OS; months Median (95% CI)**	18.2 (16.6, NR)	15.6 (12.7, NR)
	ITT HR (95% CI) P-value	0.76 (0.48, 1.21) p=not significant	
	Crossover (%)	57	
	RPSFT-adjusted HR (95% CI)	0.55 (0.21, 1.43)	

Dabrafenib has shown significantly improved efficacy compared to dacarbazine in the BREAK-3 study. Median PFS was 6.9 months for dabrafenib compared to 2.7 months for dacarbazine. Dabrafenib was associated with a statistically significant reduction in the relative risk for progression or death of 63%. Median overall survival for dabrafenib was also improved versus dacarbazine (18.2 months versus 15.6 months) but this was not statistically significant, as is evidenced by the wide confidence intervals. Adjustment for crossover suggests a reduction in the risk of death verus dacarbazine of 45%, although the confidence intervals remain wide because the RPSFT method utilises the p-value from the ITT population.

The results of BREAK-3 confirm that dabrafenib is an effective treatment which significantly improves PFS. Dabrafenib is also associated with clinically relevant reductions in the risk of death versus dacarbazine

Comparative efficacy

There are no head-to-head data for dabrafenib versus vemurafenib therefore indirect treatment comparisons (ITCs) were necessary. This was deemed appropriate given the similarity of the underlying trials. Results of the ITCs for PFS and OS outcomes are summarised in Table 2 below and are utilised in the economic base case. Dabrafenib demonstrated comparable PFS and OS when indirectly compared with vemurafenib,

evidenced by confidence intervals that cross one. The impact of assuming a class effect was therefore explored through sensitivity analysis in the economic modelling.

Table 2. ITC PFS and OS HRs for dabrafenib versus vemurafenib

Treatment	Control	PFS HR (95% CI)	OS HR* (95% CI)
Dabrafenib	Vemurafenib	0.97 (0.59-1.60)	0.86 (0.32-2.29)

HR<1 is in favour of treatment
*Analyses use crossover-adjusted OS HRs (RPSFT method), including for vemurafenib (BRIM-3 allowed patients to crossover from dacarbazine upon progression and RPSFT adjustment of OS results was undertaken as part of the NICE appraisal)

Safety

Dabrafenib is associated with a manageable safety profile. Notably, pyrexia was common with dabrafenib, although the maximum severity of pyrexia in BREAK-3 was Grade 3 which occurred in only 3% of patients.[3] Although there are no head-to-head data, dabrafenib appears to be associated with less phototoxicity and a lower incidence of certain types of hyperproliferative skin toxicities than vemurafenib. Photosensitivity can have a significant effect on quality of life[15-17] and is not common with dabrafenib.

Economic evaluation

A three state partitioned survival model (progression-free survival (PFS), post-progression survival (PPS) and death) projected the expected clinical and economic outcomes for previously untreated $BRAF^{V600}$ mutation-positive metastatic melanoma patients assumed to receive treatment with dabrafenib, vemurafenib or dacarbazine. This approach is common in HTAs of oncology treatments and was chosen as it was most suited to the underlying clinical data. A 30-year time horizon was employed to represent a lifetime and the base case assumes no additional benefit of experimental treatment over control beyond the end of follow-up in BREAK-3.

Empirical data from the BREAK-3 study were the starting point for modelling. PFS and OS for vemurafenib were modelled as proportional hazards versus PFS and OS for dabrafenib, utilising results from the indirect treatment comparison (OS adjusted for cross-over). Outcomes were measured in terms of quality adjusted life years (QALYs) based on individual residual life expectancy data and health related quality of life (EQ-5D) assessed in BREAK-3. The incremental cost components were BRAF testing, drug acquisition costs, drug administration costs, pre- and post-progression monitoring/ supportive care costs, costs of treating adverse events and the costs of post-study anti-cancer therapies.

Patient access scheme (PAS)

GSK has submitted a patient access scheme to PASLU to support this submission. The impact of the proposed scheme has been incorporated into the base case assessments and is reported alongside results using the dabrafenib list price. [redacted]

Results

Base case pairwise and incremental results using the dabrafenib list price and PAS price are provided in Tables 3-6.

At its list price dabrafenib is associated with ICERs of [redacted] versus dacarbazine and vemurafenib respectively. Probabilistic sensitivity analysis demonstrates that dabrafenib, at a threshold of £30,000/QALY, would be cost-effective in 1% of cases versus dacarbazine and in 24% of cases versus vemurafenib.

Base case results incorporating the PAS for dabrafenib found dabrafenib to be marginally more effective ([redacted]) but also marginally more costly [redacted] than vemurafenib, resulting in an ICER versus vemurafenib of £11,028/QALY. Dabrafenib is more costly as a result of its slightly longer PFS which results in a longer treatment duration and greater treatment costs. In a sensitivity analysis where a class-effect was assumed (equal PFS and OS), dabrafenib was associated with similar costs [redacted] and equal QALYs to vemurafenib. This small difference in cost is attributable to differences in the cost of treating adverse events. Probabilistic sensitivity analysis for the base case suggested that at a threshold of £30,000/QALY, dabrafenib would be cost-effective versus vemurafenib in 56% of cases.

The base case ICER for dabrafenib (at its PAS price) versus dacarbazine (a comparison that meets end of life criteria) was £49,019/QALY. This is within the range of ICERs deemed most plausible by the appraisal committee during the appraisal of vemurafenib.

Table 3. Base case results (list price)

	Dabrafenib	Dacarbazine	Vemurafenib
Technology acquisition cost	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Difference in total costs	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio			

Table 4: Base case results (PAS price)

	Dabrafenib	Dacarbazine	Vemurafenib
Technology acquisition cost	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Difference in total costs	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]
ICER	N/A	£49,019	£11,028
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio			

Table 5. Incremental cost-effectiveness results (list price)

Technology (and comparators)	Total cost	Total QALY	Incremental cost	Incremental QALY	ICERs versus baseline	Incremental analysis
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6. Incremental cost-effectiveness results (PAS price)

Technology (and comparators)	Total cost	Total QALY	Incremental cost	Incremental QALY	ICERs versus baseline	Incremental analysis
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	£60,980	£60,980
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	£49,019	Extended Dominance
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios						

Conclusion

Dabrafenib is an effective treatment that significantly improves PFS and is associated with clinically relevant reductions in the risk of death versus dacarbazine. Results of indirect treatment comparisons demonstrate comparable PFS and OS benefits to those achieved with vemurafenib, the current standard of care. A positive recommendation for dabrafenib will provide patients and clinicians with the choice of a cost-effective BRAF inhibitor that offers a different side effect profile to the current standard of care, at negligible additional cost to the NHS.

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.

The following technology is under assessment:

Generic name: dabrafenib (mesilate)

Brand name: Tafinlar®

Approved name: Tafinlar® 50mg and 75mg hard capsules

Therapeutic class: Antineoplastic agents – Protein kinase inhibitor. ATC Code: L01XE15.

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

The mitogen-activated protein kinase (MAPK) pathway (also known as the RAS/RAF/MEK/ERK pathway) plays a critical role in regulating normal cell growth, differentiation and survival. Dysregulation of this pathway due to genetic mutations or modifications that cause its constitutive activation contribute to the development of many cancers.[1,2] Approximately 50% of melanoma cases are believed to be caused by a mutation of a BRAF protein on the MAPK pathway which results in constitutive activation of the pathway.

Dabrafenib is an orally bioavailable, reversible, ATP-competitive inhibitor that selectively inhibits $BRAF^{V600}$ kinase activity. The mutated $BRAF^{V600}$ enzyme is found in around half of malignant melanomas where it drives abnormal proliferation and promotes cell survival.[3,4]

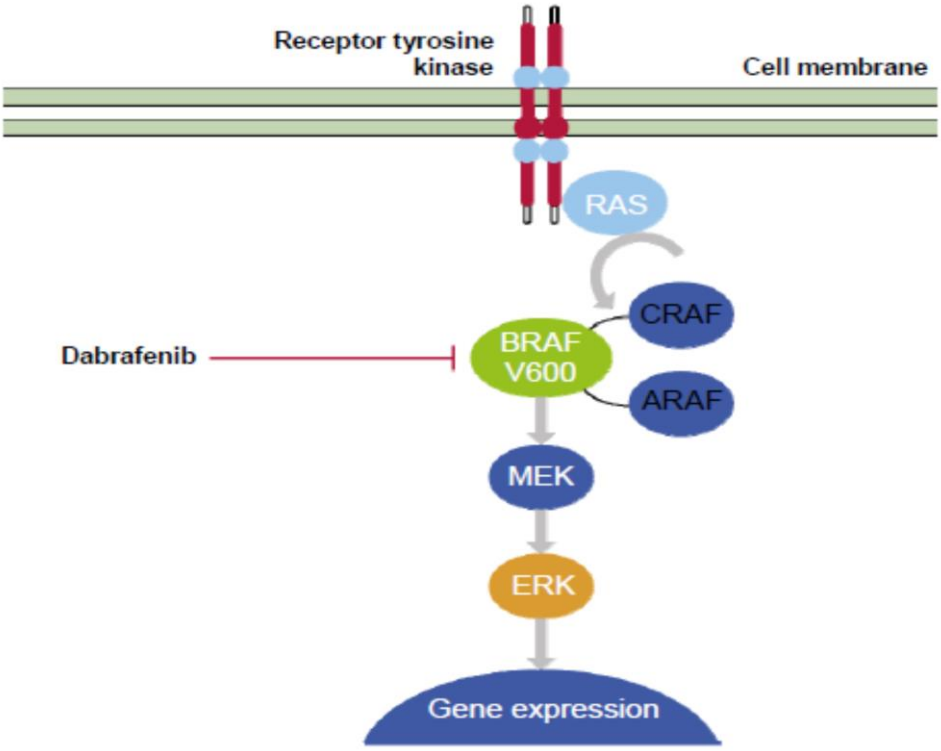


Figure 1 Mitogen-activated protein kinase (MAPK) signalling pathway

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).

Dabrafenib was granted marketing authorisation by the European Medicines Agency (EMA) on 26th August 2013 for treatment in monotherapy for adult patients with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation.

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 marketing authorisation).

Overall, the EMA considered that the BREAK-3 pivotal trial for dabrafenib monotherapy was appropriately designed and while there were no dose-finding trials, the rationale for the dose selection was accepted. The EMA concluded that a clinically relevant effect of dabrafenib was shown in $BRAF^{V600}$ mutation-positive patients with unresectable or metastatic melanoma. PFS results were considered to be robust and consistent in all sensitivity and subgroup analyses. The overall toxicity

profile was deemed acceptable and the related SAEs considered being mostly manageable. Dabrafenib is restricted to use in patients with $BRAF^{V600}$ mutation-positive disease as safety and efficacy has not been established in BRAF wild-type melanoma.

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

Dabrafenib is indicated in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation.

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.

The following table provides details of current ongoing trials relating to the above indications:

Trial number/name	Study design	Intervention	Comparator	Population	Endpoints	Status	Publication/Presentation
BREAK-3 BRF113683 NCT01227889	Phase III Open-label Randomised	Dabrafenib 150mg b.d. (n=187)	Dacarbazine 1000mg/m^2 every 3 weeks (n=63)	Patients with previously untreated metastatic (stage IV or unresectable stage III) BRAF^{V600E}-mutation positive melanoma	1^0: PFS (investigator-assessed) 2^0: PFS (independent review); OS, ORR; DoR; HRQoL; safety & tolerability	Ongoing Latest clinical cut-off: Dec 2012 Final OS analysis to be conducted when 70% of subjects have died.	Hauschild *et al*. Lancet 2012[5] (Clinical data cut-off: 19 Dec 2011) Hauschild et al. Abstract #9013. American Society of Clinical Oncology, 2013[6] (Clinical data cut-off: 25 June 2012, Dec 2012)
BRF113220 (Part C) NCT01072175	Phase II Open-label 4-part study Part C (randomised)	Dabrafenib 150mg b.d. *plus* Trametinib 2mg o.d. (n=54) Dabrafenib 150mg b.d. *plus* Trametinib 1mg o.d. (n=54)	Dabrafenib 150mg b.d. (n=54)	Patients with BRAF$^{V600E/K}$-mutation positive metastatic melanoma, with up to one prior chemotherapy for advanced/ metastatic disease	1^0: PFS, ORR, DoR, incidence of SCC, safety 2^0: OS, pharmaco-kinetics	Part D ongoing Clinical cut-off for final analysis of part C: 31 May 2012. Updated OS analysis in 29 March 2013	Flaherty *et al*. NEJM 2012[7] (Clinical data cut-off: 31 May 2012) Daud et al. Society of Melanoma Research, 2013.[8] (Clinical data cut-off: 29 March 2013)
COMBI-D MEK115306 NCT01584648	Phase III Double-blind Randomised	Dabrafenib 150mg b.d. *plus* Trametinib 2mg o.d. (n=211)	Dabrafenib 150mg b.d. *plus* Placebo (n=212)	Patients with previously untreated metastatic (stage IV or	1^0: PFS (investigator-assessed) 2^0: OS, ORR;	Ongoing Headline interim results (Aug 2013 cut	N/A

				unresectable stage III) BRAF$^{V600E/K}$-mutation positive melanoma	DoR; safety & tolerability Exploratory: HRQoL; pharmaco-kinetics; biomarkers	off) – Jan 2014 Further interim data release planned May 2014; Median OS data expected in 2015	

Key: PFS=Progression-free survival; DoR=Duration of response; HRQoL=Health-related quality of life; ORR=Objective response rate; OS=Overall survival; SCC = squamous cell carcinoma.

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

Dabrafenib monotherapy was made commercially available in the UK on 1st January 2014.

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

On 29th May 2013, the FDA approved dabrafenib under the brand name Tafinlar® for use as a single-agent for the treatment in monotherapy of patients with unresectable or metastatic melanoma with a $BRAF^{V600E}$ mutation as detected by an FDA-approved test. Dabrafenib was also approved by Health Canada on July 24th, 2013 and in Australia by the Therapeutics Goods Administration (TGA) on 3rd September 2013 for patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma.

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?

GSK expects to make a submission for dabrafenib in $BRAF^{V600}$ mutation-positive unresectable/metastatic melanoma to the Scottish Medicines Consortium (SMC) during Q3 2014, to allow guidance on the use of the product to be issued to NHSiS during Q4 2014.

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>Hard capsules (Opaque dark red 50mg; Opaque dark pink 75mg)</td></tr>
<tr><td>Acquisition cost (excluding VAT)</td><td>NHS list price dabrafenib: 28 day supply @ £5,600 (28x75mg: £1,400 | 28x50mg: £933.33)
[redacted]</td></tr>
<tr><td>Method of administration</td><td>Oral. Capsules should be swallowed whole with water; not be chewed or crushed and taken at least 1 hour before or 2 hours after a meal; leave an internal of ~12 hours between doses and take at similar times each day</td></tr>
<tr><td>Doses</td><td>Recommended starting dose: 150mg (two x 75mg capsules) twice daily. Total daily dose = 300mg</td></tr>
<tr><td>Dosing frequency</td><td>Twice daily</td></tr>
<tr><td>Average length of a course of treatment</td><td>Taken continuously until the patient no longer derives benefit or the development of unacceptable toxicity</td></tr>
<tr><td>Average cost of a course of treatment</td><td>[redacted]</td></tr>
<tr><td>Anticipated average interval between courses of treatments</td><td>N/A. One course per patient, taken continuously until the patient no longer derives benefit or the development of unacceptable toxicity</td></tr>
<tr><td>Anticipated number of repeat courses of treatments</td><td>Repeat courses are not anticipated; patients are treated until they no longer derive benefit or develop unacceptable toxicity</td></tr>
<tr><td>Dose adjustments</td><td>Management of adverse reactions may require dose reduction, or treatment interruption or discontinuation.

Table 1: Recommended dabrafenib dose level reductions
<table>
<tr><th>Dose Level</th><th>Dose/Schedule</th></tr>
<tr><td>Full dose</td><td>150 mg b.d.</td></tr>
<tr><td>First reduction</td><td>100 mg b.d.</td></tr>
<tr><td>Second reduction</td><td>75 mg b.d.</td></tr>
<tr><td>Third reduction</td><td>50 mg b.d.</td></tr>
</table></td></tr>
</table>

Table 2: Dabrafenib dose modification schedule based on the grade of any AEs

Grade (CTC-AE)*	Recommended dabrafenib dose modifications
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0-1 and reduce by one dose level when resuming therapy
Grade 4	Discontinue permanently, or interrupt therapy until grade 0-1 and reduce by one dose level when resuming therapy

* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. Dose should not exceed 150mg twice daily.

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma.

Therapy should be interrupted if the patient's temperature is ≥38.5^{o}C. Patients should be evaluated for signs and symptoms of infection.

Further details are provided in the dabrafenib SmPC relating to specific AE management.

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.

Not applicable.

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

Dabrafenib is a targeted therapy for the treatment of $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma. $BRAF^{V600}$ mutations are found in approximately 50% of melanomas[10]. Before taking dabrafenib, patients must have confirmation of $BRAF^{V600}$ mutation status using a validated test.

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

Since dacarbazine was the standard of care for treatment of metastatic melanoma at the time that the BREAK-3 study was conducted, and therefore the most appropriate comparator treatment versus dabrafenib, we will first explore the additional monitoring requirements for dabrafenib over that of dacarbazine. The emergence of vemurafenib as the new standard of care in recent years has revealed some similarities in the side effect profile to that of dabrafenib, plus some important differences, which we will also discuss in turn below.

The Summary of Product Characteristics for dabrafenib highlights the specific monitoring requirements below as special warnings and precautions.

Some of the adverse events with dabrafenib that may overlap with vemurafenib, but that are not specified as special warnings and precautions with dacarbazine, include:[11,12]

- Cases of cutaneous squamous cell carcinoma (including keratoacanthoma) have been reported in patients treated with dabrafenib. It is recommended that skin examination be performed prior to initiation of therapy with dabrafenib and monthly throughout treatment and for up to six months after treatment for cuSCC. Monitoring should continue for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy

- New primary melanomas have been reported in dabrafenib clinical trials. Monitoring for skin lesions should occur as described for cuSCC. Patients should also be monitored for non-cutaneous malignancy during therapy as clinically appropriate, following initial head and neck examinations and chest/abdominal CT scans prior to initiation of therapy

- Ophthalmologic reactions, including uveitis and iritis have been reported. Patients should be routinely monitored for visual signs and symptoms (such as, change in vision, photophobia and eye pain) while on therapy

- QT prolongation: One subject in the integrated safety population experienced a QTcB > 500 ms and only 3 % experienced worst-case QTc prolongation of > 60 msec. Electrocardiogram (ECG) and electrolytes (including magnesium) must be monitored in all patients before treatment with dabrafenib, after one month of treatment and after dose modification. Further monitoring is recommended in particular in patients with moderate to severe hepatic impairment monthly during the first 3 months of treatment followed by every 3 months thereafter or more often as clinically indicated. Initiation of treatment with dabrafenib is not recommended in patients with QTc > 500 msec. If during treatment the QTc exceeds 500 msec, dabrafenib treatment should be temporarily interrupted, electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur once the QTc decreases below 500 msec and at a lower dose as described in Table 2. Permanent discontinuation of dabrafenib treatment is recommended if the QTc increase meets values of both > 500 msec and > 60 msec change from pre-treatment values

The use of dabrafenib for $BRAF^{V600}$ mutation-positive metastatic melanoma is unlikely to require additional monitoring beyond that associated with the use of the BRAF-inhibitor, vemurafenib. This monitoring would generally require regular patient review during the time period when the treatment is being administered as cycles of therapy, as would be customary for any treatment for cancer, and in particular when compared to the management of vemurafenib therapy. Therefore there should be no extra cost consideration when managing patients under tretament with dabrafenib compared to vemurafenib.

Specific monitoring requirements associated with dabrafenib that are not specified as special warnings and precautions with vemurafenib, include:[12,13]

- Pancreatitis has been reported in dabrafenib-treated subjects. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis.

- Fever has been reported in clinical trials. In 1 % of patients in clinical trials, serious non-infectious febrile events were identified as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency or pre-renal origin in subjects with normal baseline renal function. The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care.

There are certain toxicities associated with vemurafenib that currently do not appear to be shared with dabrafenib as a special warning or precaution e.g. photosensitivity and severe hypersensitivity reactions.[12,13]

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?

There are no other specific therapies that need to be administered in conjunction with dabrafenib. However, patients may require concomitant medications for the management of disease-related symptoms or treatment-related side effects (see Section 2.8).

2 Context

- Melanoma is an aggressive form of skin cancer arising from malignantly transformed melanocytes, and accounts for >80% of deaths associated with skin tumours.
- Approximately 50 to 60% of melanomas harbour activating mutations in the BRAF oncogene.
- The incidence of melanoma is increasing worldwide; the most common risk factors are pale sun-sensitive skin and the presence of increased numbers of melanocytic naevi (moles).
- Over 11,000 new cases of melanoma are diagnosed in England and Wales each year, and around 2,000 people die from the disease. Mean age of diagnosis is 50 years but about a fifth of cases present in younger adults.
- Surgical excision is the standard of care for primary melanomas. However, 20% of primary tumours will progress to metastatic disease which carries a poor prognosis, median survival being only 6-9 months in untreated patients.
- Patients with metastatic disease are generally symptomatic with a consequently low quality of life.
- Dacarbazine has historically been the standard first-line therapy for metastatic melanoma; however, response rates are low and a survival benefit has not been reported.
- Vemurafenib, a selective BRAF-inhibitor, has recently been approved by NICE for the treatment of BRAF v600 mutation-positive unresectable or metastatic menlanoma.
- Dabrafenib offers an alternative BRAF inhibitor that appears to have similar efficacy but a different safety profile to vemurafenib.

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 one type of skin cancer, the others being basal cell carcinoma and squamous cell carcinoma. It results from the abnormal growth of melanocytes (melanin-producing cells) and approximately 90% of melanomas have a cutaneous origin.[14,15] Although representing less than 5% of skin cancers overall, malignant melanoma is the most aggressive form of skin cancer and can be fatal, particularly if the disease is not detected and treated at an early stage.[16]

The incidence of melanoma has been rising steadily in Western populations for several decades. This may be partly attributed to increased surveillance and early detection, as well as changes in diagnostic criteria, but also may reflect changes over time in people's sun-related behaviour,[16] including the use of sun-beds.

Malignant melanoma is currently the fifth most common cancer in the UK, accounting for 4% of all new cancer cases.[17] Incidence rates in the UK have risen sharply from 11 cases per 100,000 population in 1999-2001 to 17 cases per 100,000 population in 2008-2010.[17] In 2010, there were 12,818 new cases of malignant melanoma diagnosed in the UK,[17] and in 2011 2,209 deaths from the disease, representing 1% of all cancer deaths (2% of all male deaths from cancer) and 80% of deaths from skin cancer.[18]

A melanoma often has a slow early growth phase, and if detected before it has spread, can be cured by surgical resection. Approximately 80-90% of melanomas are diagnosed as localised tumours (Stages I and II) without regional or metastatic spread and can be dealt with in this way.[19-21] However, melanoma is an unpredictable tumour and may spread to nearby lymph nodes (Stage III) or to other parts of the body (Stage IV), most commonly the skin or subcutaneous soft tissues, lung, and brain.[19] Metastatic disease occurs in about 20% of patients with malignant melanoma.[20] An estimated 16.5% of those with primary melanoma relapse with regional or distant recurrence, and 2-8% of people already have metastatic disease when diagnosed.[22,23] The prognosis in these cases is poor (see Section 2.3). Patients with metastases to the brain, lung and other visceral sites have a poorer survival than those with metastases in the skin or subcutaneous tissues.[19]

Health-related quality of life (HRQoL) is significantly impacted in melanoma patients across all disease stages, and patients with advanced disease have worse HRQoL than those with lower-stage disease.[24] The impact of melanoma on HRQoL is comparable to that observed in other cancers.[25] The most common HRQoL impairments reported are pain and fatigue with a concomitant decrement in physical and emotional functioning.[26]

Healthcare resource utilisation and costs associated with advanced melanoma are also high.[27] A retrospective European study found that 28% of all advanced melanoma patients in the UK had at least one overnight hospital stay each year, with the majority of hospital episodes related to toxicity during active therapy or disease progression during supportive care.[28] The hospitalisation cost per patient per year in the UK was €3225 (£[2013] 2747)and the outpatient costs were €782 (£[2013] 666) per person per visit.[28] A study in England (2009) estimated the total annual cost attributable to malignant melanoma to be £144 million, including healthcare and indirect morbidity and mortality costs.[29]

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

We estimate the maximum number of patients covered by this therapeutic indication (adults with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation) to be 990 incident cases per annum (comparable to the manufacturer's estimates in the vemurafenib NICE submission), and so a sub-population of the metastatic melanoma population, using the following method:

		Source
Population of England & Wales	56,567,800	Office for National Statistics (2012 data)[30]
Incidence of melanoma in the UK = 20.6 per 100,000 population (crude incidence)	11,653	Cancer Research UK[17]
Proportion with unresectable Stage III/Stage IV	2,330	Lacy *et al*, Clinical Medicine

disease = 20%*		(Journal of the Royal College of Physicians)[20]
BRAF^{V600} mutation-positive = 50%	1,165	Long *et al*, J Clin Oncol 2011[10]
Excluding patients entered into clinical trials = 85% (i.e. 15% entered into clinical trials)	990	Vemurafenib NICE submission[31]
Total eligible population per annum	**990****	

* includes progressed from earlier stages, plus new presentations of unresectable Stage III/Stage IV metastatic disease

**assumes all patients are diagnosed, all patients are fit for treatment and all receive this new targeted therapy

This estimate does not account for market share and so represents a maximum number of eligible patients.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Melanoma has a substantial impact on life expectancy since it typically affects a younger cohort of patients compared with many other cancers. A UK study quantified the years of potential life lost (YPLL), reporting an average of 15 YPLL per death from malignant melanoma and ranking it fourth among cancers examined.[32,33] Assuming the population in this study to be representative of the overall UK population, the total YPLL lost in the UK is likely to be considerable given that there are approximately 2,000 deaths from melanoma each year.

For stage III disease, 5-year survival rates can vary from 40 to around 80%, depending on the number of lymph nodes involved and the nodal metastatic burden.[19] Stage IV melanoma has an extremely poor prognosis and is largely refractory to conventional chemotherapy. Median survival times of 6 to 18 months after stage IV diagnosis are reported, depending on the organs involved.[19,21] Patients with disseminated disease have 5-year survival rates ranging from 20% to just 5%.[34]

Melanoma has a marked propensity to metastasize to the brain. Up to 50% of patients develop brain metastases during the course of their illness and 20% have them at first presentation of metastatic disease.[35,36] People with melanoma brain metastases have a life expectancy of only 3–5 months.[21] This therefore represents a unique subgroup of metastatic melanoma patients with a particularly poor prognosis.

The availability of vemurafenib represented a step change in the management of BRAF^{V600} mutation-positive malignant melanoma, and the discovery that the MAPK pathway is frequently activated in human cancers opened a door to the development of such targeted therapies. As a palliative treatment, BRAF inhibitors extend survival compared to dacarbazine, although even with vemurafenib treatment, life-expectancy is still under two years.[37-39] The available population statistics will not yet reflect the changing prognosis of patients resulting from the availability of the new therapies, however, the pivotal study for vemurafenib suggests a median overall survival in vemurafenib-treated patients of 13.2 months.[38]

2.4 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.

There are several recent technology appraisals of melanoma treatments:

- In December 2012, NICE published Technology Appraisal Guidance recommending vemurafenib (Zelboraf®, Roche) as a treatment option for $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma, on the condition that the manufacturer provides vemurafenib with the discount agreed with the Department of Health.[40]
- At a similar time, Technology Appraisal Guidance was also issued recommending ipilimumab (Yervoy®, Bristol-Myers Squibb), a monoclonal antibody which enhances T-cell activation, as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, provided the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.[41] This guidance is for a different patient population than that considered in the present submission.

In 2006, NICE published guidance on the development of cancer services for people with skin tumours including melanoma. This document focused primarily on the organisation of services. It pre-dated the emergence of targeted therapies and recommended non-surgical treatment options including dacarbazine and interferon-α.[42] A NICE evidence update, published in October 2011, made reference to key clinical trials for vemurafenib and ipilumumab.[43]

A NICE clinical guideline for the assessment and management of malignant melanoma is in development and is due for publication in April 2015.

There are several other relevant non-NICE guidelines although all were published before the introduction of targeted therapies.[21,44-46]

2.5 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.

Systemic therapy is now considered the mainstay of treatment for patients with stage IIIc (inoperable regional metastases) or stage IV (distant metastases) disease.[21] The goals of such treatments are to delay disease progression and palliate symptoms whilst minimising toxicity and detriment to quality of life.[47,48]

Since receiving a positive recommendation from NICE in December 2012, vemurafenib has become the standard of care for $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma,[40] largely replacing dacarbazine. It is estimated

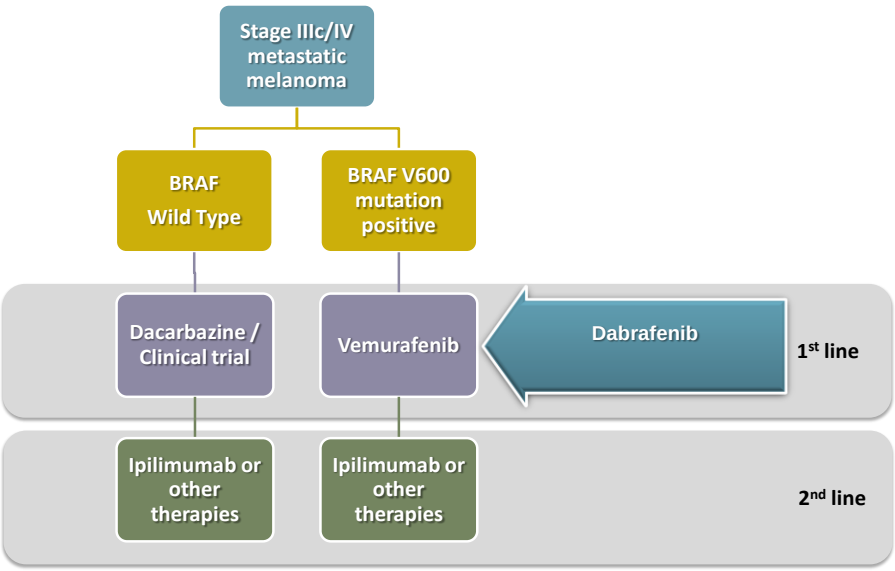
that approximately 92% of metastatic melanoma patients who tested BRAF positive were receiving first-line vemurafenib.*

Dabrafenib is an alternative BRAF inhibitor with a similar efficacy profile but a different safety profile to vemurafenib.[49-51] Both agents achieve tumour response rates of approximately 50% and significantly improved progression-free survival (PFS) compared with dacarbazine.[5,37]

People with BRAF-wild type metastatic melanoma continue to receive first-line therapy with dacarbazine or may be entered into a clinical trial with an experimental therapeutic option. Following the positive NICE recommendation for ipilimumab, all patients whose disease progresses on first-line treatment may be considered for ipilimumab[41] or other immunotherapies in the context of clinical trials.[21] It is unclear at this stage how the first line indication for ipilimumab will affect clinical practice.

Figure 2 illustrates the place of dabrafenib in the treatment pathway for metastatic melanoma.

Figure 2. Treatment algorithm for metastatic melanoma



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

We do not anticipate any issues or uncertainty around the use of the current standard of care; vemurafenib is the subject of positive NICE guidance and has a widespread uptake in its recommended and indicated patient population.

A draft service specification for certain skin cancers, including melanoma, was issued by the NHS Commissioning Board (now NHS England) in December 2012. This described the delivery of services through a specialist skin multidisciplinary team,

* IMS, Oncology Analyzer. Vemurafenib monotherapy usage in 1L BRAF mutation positive stage IV metastatic melanoma patients. Q4 2012.

with some elements delivered through supra-network multidisciplinary teams.[52] A final service specification is awaited and it remains to be seen how this is implemented in practice.[*]

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

The key comparator for dabrefenib in this setting is vemurafenib, the current standard of care for patients with $BRAF^{V600}$ mutation-positive metastatic melanoma. Vemurafenib was deemed to be a cost-effective alternative to dacarbazine (the previous standard of care for this patient group) by NICE in December 2012 and 92% of eligible patients in the UK are currently receiving this BRAF inhibitor monotherapy.[†] We will also provide a comparison versus dacarbazine as requested by NICE in the scope for this appraisal.

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

- Non-steroidal anti-inflammatory drugs (NSAIDs), e.g. ibuprofen (preferred), or paracetamol/acetaminophen, to manage pyrexia and other non-infectious febrile events associated with dabrafenib treatment. If the patient's temperature is ≥ 38.5°C, therapy with dabrafenib should be interrupted
  - Oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient;
  - If necessary, signs and symptoms of infection should be treated in line with local practice. Upon resolution of pyrexia dabrafenib should be restarted with appropriate anti-pyretic prophylaxis
- Low-grade hyperkeratosis would typically be managed with the use of topical steroid cream, with the addition of an oral antihistamine or a short-course of oral steroids for higher grade events.
- Management of PPE requires the use of emollient creams; urea-based creams are thought to be particularly helpful.
- Cases of SCC or keratoacanthoma should be managed by dermatological excision which would normally be performed as an outpatient procedure mainly under local anaesthetic. In the BREAK-3 trial, all cases were treated with surgical curettage and reported as resolved; no patients required dose modification or discontinuation of treatment due to these events.
- Arthralgia can be managed using simple analgesics (paracetamol or NSAIDs) and the application of topical NSAID creams.

[*] https://www.engage.england.nhs.uk/consultation/ssc-area-b

[†] IMS, Oncology Analyzer. Vemurafenib monotherapy usage in 1L BRAF mutation positive stage IV metastatic melanoma patients. Q4 2012.

2.9 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.

Dabrafenib treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. Before initiation of dabrafenib, patients must have confirmation of a $BRAF^{V600}$ mutation using a validated test. This requires histopathological services to test for the BRAF mutation on tumour excision or biopsy samples. The requirement for testing with these new technologies will be no greater than it is currently. A one-time cost of BRAF mutation testing is included for each patient entering the model. Per patient test costs are estimated by dividing the cost per test (£95) by one minus the estimated percent of patients who test positive, such that BRAF positive patients in the model carry the costs of testing all metastatic melanoma patients. This accounts for the fact that all patients are tested but only those who test positive will be treated.

Dabrafenib is an oral therapy and can be self-administered by patients at home. As such, there will be limited impact on pharmacy resource. Our economic model assumes a dispensing cost of £13.40 for each prescription (based on the cost of 15 minutes of hospital pharmacist time). A 28-day supply of dabrafenib is assumed to be prescribed every 4 weeks (28 days); dabrafenib is available in 7-day packs.

Medication costs in the economic model have been taken from the 2013/14 British National Formulary (BNF 66). The cost of vemurafenib is calculated assuming the discounted unit price as provided by the manufacturers to GSK by NICE in November 2013.

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

The introduction of dabrafenib will not require any additional infrastructure over and above that required to treat patients with vemurafenib.

3 Equality

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

To our knowledge there are no equality issues that could impact on this appraisal.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

BRAF inhibitors, as a class, can be considered a step-change in the management of metastatic melanoma[53]. This disease has lacked treatment innovation for many decades and traditionally viewed as one with a high unmet medical need. Until very recently, the standard first-line management of metastatic melanoma irrespective of BRAF mutation status was with dacarbazine, an intravenously administered cytotoxic agent, that is associated with poor response rates and no survival benefit[54,55].

Approximately 50% of melanomas have an activating mutation in the BRAF gene[10], and thus, the BRAF receptor represents a rational therapeutic target. Like vemurafenib which has recently been approved by NICE for the treatment of patients with $BRAF^{V600}$-mutated metastatic melanoma[53], dabrafenib achieves high response rates and prolongs PFS compared with dacarbazine[5] and is more convenient to administer due to its oral formulation.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

It is difficult to determine whether there may be any significant or substantial health-related benefits that will not be captured in the QALY calculation. EQ-5D assessments of utility are inputs in the economic model that will underpin this assessment. This is stated to be NICE's preferred measure of health-related quality of life (HRQoL). There is some discussion in current literature about the specificity of the EQ-5D measure for skin conditions (including melanoma),[56] although the methodology of the underlying study is unclear and it not obvious how conclusions were reached. If there are shortcomings of the EQ-5D in this regard, it is difficult to anticipate their impact in this assessment. It is possible that QALY differences between drugs with different skin toxicities (e.g. dabrafenib and vemurafenib, where there are notable reductions in some skin toxicities observed with dabrafenib) may be underestimated. However, the utilities implemented in this appraisal (derived from EQ-5D assessments in the underlying monotherapy trials) are comparable to those

accepted as appropriate in the NICE appraisals of both vemurafenib and ipilimumab, [40,41] confirming their face validity.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable.

5 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 advanced or metastatic BRAF^{V600} mutation-positive melanoma	Adults with previously untreated advanced or metastatic BRAF^{V600} mutation-positive melanoma.	There is insufficient evidence from the clinical trials with which to build an economic argument for the use of dabrafenib in people with BRAF^{V600} mutation-positive metastatic melanoma who have received prior therapy
Intervention	• Dabrafenib monotherapy	• Dabrafenib monotherapy	As per scope
Comparator(s)	For people with previously untreated melanoma: • dacarbazine (or temozolomide for people whose melanoma has metastasised to the brain) • vemurafenib For people with previously treated melanoma: • dacarbazine (or temozolomide for people whose melanoma has metastasised to the brain) • ipilimumab • vemurafenib	Previously untreated patients • Vemurafenib • Dacarbazine	• There is insufficient evidence from the clinical trials to build economic arguments for these treatments: ○ versus dacarbazine, ipilumumab and vemurafenib in people with BRAF^{V600} mutation-positive metastatic melanoma who have received prior therapy: ○ versus temozolomide in patients whose malignant melanoma has metastasised to the brain

Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life	The outcome measures include: • progression-free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life	As per scope
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	• Cost-effectiveness will be expressed in terms of an incremental cost per quality-adjusted life year, over a lifetime horizon • Costs will be considered from an NHS and PSS perspective • Medication costs (for interventions and comparators) will incorporate available patient access schemes	As per scope
Subgroups to be considered	None specified	Adults with previously untreated advanced or metastatic $BRAF^{V600}$ mutation-positive melanoma.	There is insufficient evidence from the clinical trials with which to build an economic argument for the use of these treatments in people with $BRAF^{V600}$ mutation-positive metastatic melanoma who have received prior

			therapy
Special considerations, including issues related to equity or equality	None specified	There are no special considerations relating to equity or equality	N/A

*Trametinib and combination therapy have been removed from the scope issued by NICE

Section B – Clinical and cost-effectiveness

6 Clinical evidence

6.1 Identification of studies

6.1.1 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 Error! Reference source not found.**.**

A systematic review was carried out to identify, report and if appropriate, meta-analyse or indirectly compare any clinical studies of relevance to this NICE appraisal. The review was conducted and reported in line with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.

- The overall objective of the original systematic review was to evaluate the relative efficacy and safety of dabrafenib, trametinib and dual therapy (dabrafenib + trametinib) compared to vemurafenib, dacarbazine ('DTIC') and, for completeness, ipilimumab and fotemustine, in the treatment of metastatic melanoma.
- Only data relating to dabrafenib (*the intervention under review*), and its comparison with vemurafenib and dacarbazine (*the comparators defined in the scope for this appraisal*) are presented in the main body of the submission.

A comprehensive search strategy was designed to retrieve relevant clinical data from the published literature; full details of the search strategy can be found in Appendix **Error! Reference source not found.**. The full systematic review report (372 pages) is available upon request.

The following electronic databases were searched from database start until 22 October 2012 – the searches were updated in October 2013 to identify additional published studies of relevance to the submission.

Data source	Service provider
MEDLINE (22 October 2012; 1980 onwards)	Embase.com http://www.embase.com/
EMBASE (22 October 2012; 1980 onwards)	Embase.com http://www.embase.com/
Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Cochrane Methodology Register (22 October 2012; 1980 onwards)	Cochrane library http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html

MEDLINE In process and other non-indexed citations (22 October 2012)	PubMed http://www.ncbi.nlm.nih.gov/sites/entrez

Only studies with the full-text in English were included in this review. Citations retrieved through the literature search were initially screened for inclusion based on their title and abstract. Citations that did not match the eligibility criteria were excluded during 'first pass', as were duplicates of citations. Full-text copies were obtained for citations that met the inclusion criteria and also where it was not possible to determine whether the study met the inclusion criteria based on the abstract alone. Full details of the search, plus search strategies and search syntax for the individual databases/sources, can be found in Appendix **Error! Reference source not found.**.

The manufacturer believes that it is unlikely that further RCTs of relevance would be detected by a more recent systematic review compared to those found within the updated search conducted in October 2013. However, one update to an exisiting study identified in the systematic review; BRF113220, was found following a review of more recent literature. This update was presented as an oral presentation at the Society of Melanoma Research congress in November 2013[8], and data pertaining to dabrafenib monotherapy that is contained within this updated presentation will be used as supportive, but not quantitative, evidence within this submission.

6.2 Study selection

6.2.1 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.

Details of the inclusion and exclusion criteria employed for the systematic review are presented in Table 3.

Table 3. Eligibility criteria for trials to be included in the systematic review

Criteria	Parameters	Rationale
Inclusion criteria	**Population** • Age: adults (≥18 years or ≥16 years if defined by author) • Gender: any • Race: any • Disease: advanced or metastatic melanoma	• Mean age of diagnosis is 50 years; approximately 20% of melanoma cases occur in young adults aged between 15 years and 39 years • Melanoma can occur both in men and women, although men are at a higher risk • Clinical trials and other studies usually enrol participants of all races to have a sample population representative of the larger population, and to reduce bias. Patients with other types of skin cancers (non-melanoma skin cancers) such as basal cell and squamous cell cancers, Kaposi sarcoma, and lymphoma of

		the skin were not included
	Intervention • Dabrafenib (GSK2118436) • Trametinib (GSK1120212) • Vemurafenib • Ipilimumab • Dacarbazine • Fotemustine	• These interventions were identified from clinical practices or from undergoing clinical trials for the treatment of metastatic melanoma
	Comparator • Any treatment from the above included list of interventions • Placebo or best supportive care • Any other chemotherapy • Any immunotherapy	• These comparators were selected to potentially enable both direct and indirect comparisons between the interventions of interest
	Outcomes of interest *Efficacy:* • Overall survival (OS) • Progression-free survival (PFS) • Overall response rate (ORR: Complete response [CR] + Partial response [PR]) • Proportion of patients with stable disease (SD), and progressive disease (PD) • Time to, and duration of, response (TTR, DoR) • Health-related quality of life (HRQoL) *Safety:* • Incidence and severity of all adverse events (AEs) • Incidence and severity of specific AEs • Withdrawals due to AEs • Withdrawals due to death • Serious adverse events (SAEs)	• These outcomes were chosen since they are frequently measured and reported in trials in metastatic melanoma • Refer to Section 6.3.5 for justification and further explanation relating to the selection of these study outcomes
	Study design • RCTs with any blinding status • Non-RCTs • Observational studies • Single arm studies	• RCTs are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of interventions. To enhance the level of evidence, studies with double-blind, single-blind, and open-label design were included • Apart from providing long term benefit data, non-RCTs were included to supplement evidence provided by RCTs. Observational studies include wider patient populations and present real-life effectiveness data
	Language restrictions	• The restriction does not limit results

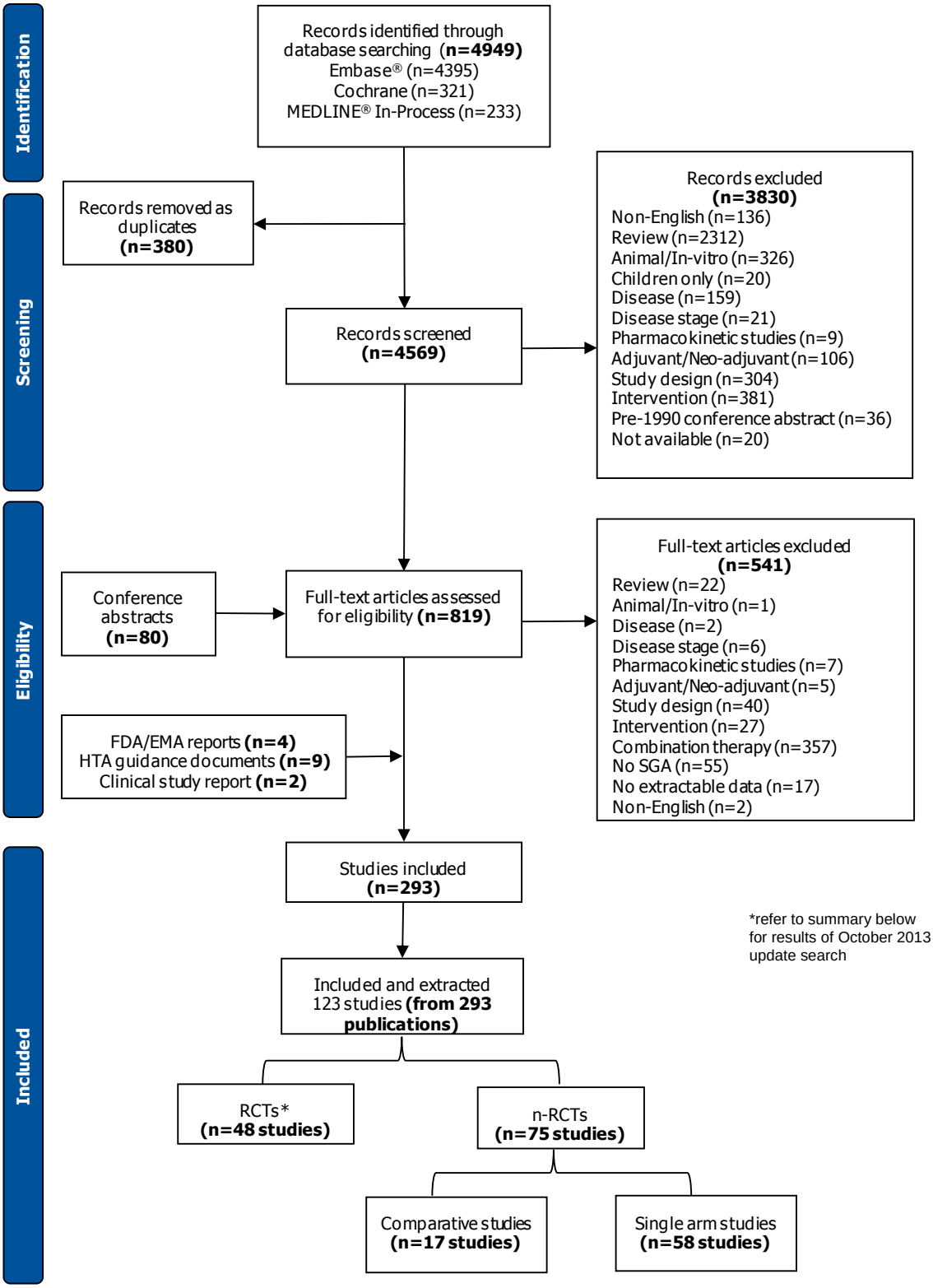
	• English only	substantially due to data availability provided in English
	Publication timeframe • 1960 to 22 October 2012 for literature searches; updated from 25 October 2013 • 2010 to 2012 for conference searching	• Studies presented at conferences are usually published in journals within three years
Exclusion criteria	• No subgroup analysis for the disease or intervention of interest • Conference abstracts published before 1990	• Studies with no subgroup data for the disease were not included, as these studies could introduce heterogeneity into the review • Studies which enrolled a mixed population of stage I, II, III, and IV melanoma were only included if there was a subgroup analysis on the stage III and/or IV patient population • Studies presented in very old conferences should have been published in journals as full text articles and been retrieved via the database searches

RCT: Randomised Controlled Trial

The literature searches were updated on 25 October 2013. To aid the appraisal process, more targeted screening for studies of interest through stricter inclusion and exclusion criteria, i.e. we only considered RCTs that involved the intervention or comparators of interest to this appraisal (See Appendix Error! Reference source not found.). The updated search revealed no additional RCTs of relevance to the decision problem.

6.2.2 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 6.2.4.

Studies were included / excluded on the basis of the criteria detailed in Table 3 above and the results of each stage of the inclusion / exclusion process, including the updated literature search of October 2013, are summarised in Figure 3.


Identification
Screening
Eligibility
Included
Records identified through database searching (n=4949)
Embase® (n=4395)
Cochrane (n=321)
MEDLINE® In-Process (n=233)
Records removed as duplicates (n=380)
Records screened (n=4569)
Records excluded (n=3830)
Non-English (n=136)
Review (n=2312)
Animal/In-vitro (n=326)
Children only (n=20)
Disease (n=159)
Disease stage (n=21)
Pharmacokinetic studies (n=9)
Adjuvant/Neo-adjuvant (n=106)
Study design (n=304)
Intervention (n=381)
Pre-1990 conference abstract (n=36)
Not available (n=20)
Conference abstracts (n=80)
Full-text articles assessed for eligibility (n=819)
Full-text articles excluded (n=541)
Review (n=22)
Animal/In-vitro (n=1)
Disease (n=2)
Disease stage (n=6)
Pharmacokinetic studies (n=7)
Adjuvant/Neo-adjuvant (n=5)
Study design (n=40)
Intervention (n=27)
Combination therapy (n=357)
No SGA (n=55)
No extractable data (n=17)
Non-English (n=2)
FDA/EMA reports (n=4)
HTA guidance documents (n=9)
Clinical study report (n=2)
Studies included (n=293)
*refer to summary below for results of October 2013 update search
Included and extracted 123 studies (from 293 publications)
RCTs* (n=48 studies)
n-RCTs (n=75 studies)
Comparative studies (n=17 studies)
Single arm studies (n=58 studies)

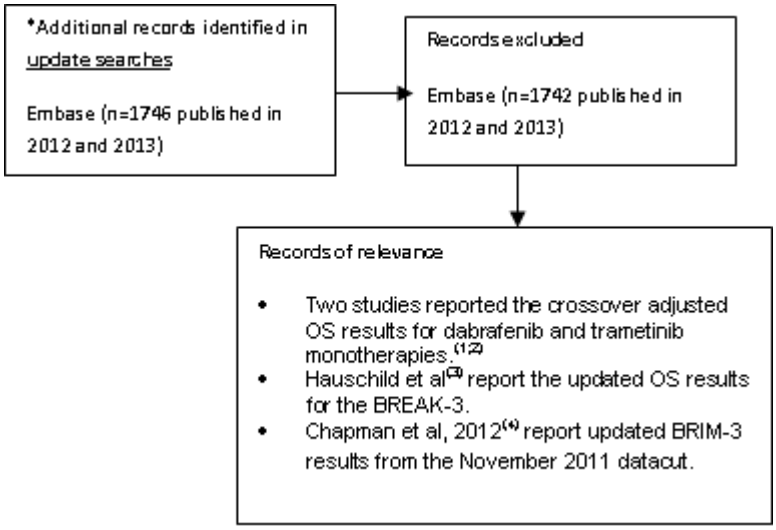


Figure 3. Clinical studies trial flow

The 48 RCTs included 28 completed studies providing data for either treatment-naïve (n=24), pre-treated patients (n=2) or a mixed population of both treatment- naïve and pre-treated patients (n=2) with metastatic melanoma, of which four studies were conducted in patients with $BRAF^{V600}$ mutation-positive melanoma; the population being considered in this submission. These include:

- One phase III trial evaluating the efficacy and safety of dabrafenib compared with dacarbazine in patients with $BRAF^{V600E}$ mutation-positive metastatic melanoma (BRF113683; BREAK-3)[5] This study provides the primary evidence for dabrafenib; as such, the design, methodology and results are presented in detail within this submission.
- One phase III trial evaluating the efficacy and safety of vemurafenib compared with dacarbazine in patients with $BRAF^{V600E}$ mutation-positive metastatic melanoma (BRIM-3)[37]. As this study has been used to conduct an adjusted indirect treatment comparison, the design, population and results are discussed further in section 6.7.
- One phase II trial in patients with $BRAF^{V600E/K}$ mutation-positive metastatic melanoma conducted in four parts where part C involved randomisation (1:1:1) of patients to one of two different dosages of dabrafenib in combination with trametinib or to dabrafenib monotherapy (BRF113220)[7] . Since the primary objective of this part of the trial was to evaluate combination therapy with dabrafenib plus trametinib versus dabrafenib monotherapy; the data for the control arm are presented as supportive evidence but have not been utilised in any quantitative analyses.

The systematic review also identified an additional 22 RCTs involving dacarbazine (either as single-agent or in combination with other agents) in treatment-naïve or pre-treated metastatic melanoma patients. Since these studies were not specifically conducted in a $BRAF^{V600}$ mutation-positive population and evaluated different dosages from those used in the control arms of the BREAK-3, and BRIM-3 studies, they could not be utilised in the adjusted indirect treatment comparison and are not presented further in this submission.

A further two RCTs involving ipilimumab were identified in pre-treated metastatic melanoma patients and one RCT involving trametinib; these studies do not contain

any data of relevance to the decision problem and are not discussed further. Further details of these studies are available in the systematic review report.

Of the 75 non-RCTs included in the systematic review, 17 were comparative studies and 58 were single-arm studies.

Two dabrafenib monotherapy studies were included among the non-RCTs identified and are presented in section 6.8 of this submission as supportive evidence.

- One phase II single-arm study evaluating dabrafenib in patients with BRAF $^{V600E/K}$ mutation-positive metastatic melanoma (BRF113710; BREAK-2). [57]
- One phase II study evaluating dabrafenib in patients with BRAF$^{V600E/K}$ mutant melanoma and asymptomatic brain metastases (BRF113929; BREAK-MB). [4]

Since the systematic review update in October 2013, interm results from a phase III trial evaluating the efficacy and safety of dabrafenib in combination with trametinib compared to dabrafenib monotherapy, in patients with BRAF$^{V600E/K}$ mutation-positive unresctable or metastatic melanoma (Combi-d)[58] has been made available on the GSK clinical trials register. These data have not yet been published. The data for the control arm are presented as supportive evidence for dabrafenib but have not been utilised in any quantitative analyses.

6.2.3 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.

Data for the dabrafenib pivotal phase III trial (BREAK-3; BRF113683) have been drawn from a number of sources, as shown in Table 4. Data for the key vemurafenib comparator trial (BRIM-3) utilised in the adjusted indirect comparison (Section 6.7) have also been drawn from a number of sources (see Table 4). Following the updated literature search in October 2013, additional data sources/publications were identified relating to existing RCTs found in the initial systematic review. These have been denoted in the table below by an asterisk (*).

Table 4. List of data sources for RCTs relevant to decision problem

Author(s)	Source	Title	Clinical cut-off date
BRF113683 (BREAK-3): Dabrafenib monotherapy			
Hauschild *et al*[5]	Lancet 2012 Jul 28:380(9839(:358-365	Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial	19 Dec 2011
Grob et al[48]*	SMR Society for Melanoma Research – 9th International Melanoma Congress. Nov 8, 2012	Dabrafenib versus dacarbazine in patients with BRAF^{V600+} advanced and metastatic melanoma in BREAK-3: Quality of Life (QOL) Analysis	19 Dec 2011
GlaxoSmithkline[59]	Clinical Study Report (CSR) for BRF113683 (2011N119043_00)	A phase III randomised, open-label study comparing GSK2118436 (dabrafenib) to dacarbazine in previously untreated subjects with BRAF^{V600} mutation-positive advanced (stage III) or metastatic (stage	19 Dec 2011

		IV) melanoma	
Hauschild *et al*[9]*	ASCO (2013) American Society of Clinical Oncology - 49th Annual Meeting. Abstract no. 9013	An update on BREAK-3, a phase III, randomised trial: dabrafenib vs dacarbazine in patients with BRAF^{V600E} positive mutation metastatic melanoma (MM)	25 Jun 2012; 18 Dec 2012
Latimer N, Abrams K. School of Health and Related Research (ScHARR)[60]*	ASCO (2013) American Society of Clinical Oncology - 49th Annual Meeting. Abstract no. 9044	Adjusting for treatment crossover in the BREAK-3 metastatic melanoma trial for dabrafenib – preliminary analysis	25 Jun 2012
BRIM-3: Vemurafenib monotherapy			
Chapman *et al*[37]	N Engl J Med. 2011 Jun 11;364:2507-2516	Improved Survival with Vemurafenib in Melanoma with BRAF^{V600E} Mutation	30 Dec 2010
National Institute for Health & Care Excellence[40]	Technology Appraisal Guidance 269	Vemurafenib for treating locally advanced or metastatic BRAF^{V600} mutation-positive malignant melanoma	December 2010; March 2011; October 2011; February 2012

Complete list of relevant RCTs

6.2.4 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.

Table 5 describes the studies of relevance to the decision problem. Two RCTs comparing dabrafenib monotherapy with other therapies were identified in the relevant patient population (patients with BRAF^{V600} mutation-positive metastatic melanoma). The pivotal phase III study, BREAK-3 (BRF113683), comparing dabrafenib with dacarbazine forms the primary evidence. The randomised part (part C) of the phase II study, BRF113220, which was set up to evaluate dual therapy (dabrafenib plus trametinib) versus dabrafenib monotherapy, provides supportive evidence for dabrafenib. There is one additional study which provides evidence for the comparator, vemurafenib, as defined in the scope for this appraisal; the BRIM-3 study[37] compared vemurafenib monotherapy with dacarbazine. This study is discussed further in relation to the adjusted indirect comparison presented in Section 6.7.2.

As discussed above, a secondary search of the Embase and Medline databases was carried out in October 2013 to identify any additional RCTs that had been published since the initial search. No further studies of relevance to this appraisal were identified.

The MEK115306 Combi-d study has not yet been published, although the primary efficacy analysis has been placed in the public domain via the GSK Clinical Study Register. As with the phase II BRF113220 study, the Combi-d study has been included to provide supportive evidence for dabrafenib monotherapy. The CSR for the Combi-d study was unavailable at the time of producing this submission.

Table 5. List of RCTs relevant to the appraisal

Study Number/ acronym	Study type	N	Intervention(s)	Comparator	Population	Primary reference	Linked pub-lications
Primary RCT							
BREAK-3 BRF113683	Phase III Open-label Randomised	250	Dabrafenib 150mg b.d. (n=187)	dacarbazine IV 1000mg/m^2 every 3 weeks (n=63)	Patients with previously untreated metastatic (stage IV or unresectable (stage IIIc) BRAF^{V600E}-mutation-positive melanoma	Hauschild *et al.* 2012[5]	Grob et al. 2012[48] Hauschild et al. 2013[9] Latimer et al. 2013[60]
Supportive RCTs							
BRF113220 (Part C)	Phase II Open-label 4-part study: Part C (randomised)	162	Dabrafenib 150mg b.d. *plus* Trametinib 2mg o.d. (n=54) Dabrafenib 150mg b.d. *plus* Trametinib 1mg o.d. (n=54)	Dabrafenib 150mg b.d. (n=54)	Patients with BRAF$^{V600E/K}$-mutation-positive metastatic melanoma, with up to one prior chemotherapy for advanced/ metastatic disease	Flaherty *et al.* 2012[7]	Long *et al.* 2012[39] Daud *et al.* 2013[8]
Combi-d **MEK115306** **ClinicalTrials.gov Identifier:** **NCT01584648**	Phase III double blind randomised	423	Dabrafenib 150mg b.d. *plus* Trametinib 2mg o.d. (n=211)	Dabrafenib 150mg b.d. *plus* Trametinib placebo (n=212)	Patients with BRAF$^{V600E/K}$-mutation positive metastatic melanoma	TBC	
Comparator							
BRIM-3	Phase III Open-label Randomised	675	Vemurafenib 150mg b.d. (n=337)	dacarbazine IV 1000mg/m^2 every 3 weeks (n=338)	Patients with previously untreated metastatic (stage IV) or unresectable (stage IIIc) BRAF ^{V600E}-mutation-positive melanoma	Chapman *et al.* 2011[37]	National Institute for Health & Care Excellence[40]

*see Table 13 and Table 27 for detail of proportion of patients crossing over to experimental arm at each data cut

6.2.5 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 BREAK-3 trial directly compares the intervention, dabrafenib, with a comparator stated in the decision problem, in this case dacarbazine. There are no head-to-head studies directly comparing dabrafenib, with the current standard of care, vemurafenib.

6.2.6 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

6.2.7 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 6.8 and key details should be presented in a table; the following is a suggested format.

Two non-RCTs are included in this submission as they provide relevant supportive data for dabrafenib as monotherapy in the patient population under consideration. See Section 6.8 for further details. These studies have not been used to contribute to any quantitative analyses.

Table 6: List of relevant non-RCTs

Study Number/ acronym	Study type	N	Intervention(s)	Population	Primary reference	Justification for inclusion
BREAK-2 BRF113710 **ClinicalTrials.gov Identifier:** **NCT01153763**	Phase II Open-label Single arm	92	Dabrafenib 150mg b.d.	Patients with previously untreated $BRAF^{V600}$-mutation positive metastatic melanoma	Ascierto *et al.* 2013[57]	Provides supportive data for dabrafenib monotherapy in relevant patient population

BREAK-MB BRF113929 **ClinicalTrials.gov Identifier:** **NCT01266967**	Phase II Open-label Single arm	172	Dabrafenib 150mg b.d.	Patients with BRAF^{V600}-mutation positive melanoma metastatic to brain	Long *et al*. 2012[4]	Provides supportive data for dabrafenib in patients with brain metastases, a population that historically has had a very poor prognosis with few available treatment options. However patients with brain metastases do not constitute a separate population to that which dabrafenib is currently licensed for.

6.3 Summary of methodology of relevant RCTs

6.3.1 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.

BREAK-3 (BRF113683)

An overview of the study design and methodology of BREAK-3 (BRF113683) is provided in Table 7. Outcome data presented in this submission are from a planned analysis conducted with a cut-off date of 19 December 2011; updated analyses conducted with a cut-off date of 25 June 2012; and an analysis of overall survival conducted for EU regulatory purposes with a cut-off date of 18 December 2012. Final overall survival data (70% mortality) are anticipated to be available during 2014.

Dabrafenib dose rationale
The dose of dabrafenib selected for the phase II and phase III trials was based on safety, pharmacokinetic and response data from a phase I study (BRF112680)[36] Doses ranging from 12 mg (12 mg once daily) to 600 mg (300 mg twice daily) were investigated and no maximum tolerated dose (MTD) was recorded. The recommended phase II dose (RP2D) of 150mg twice daily (b.d.) was selected because a minimum increase in exposure was noted with 200mg b.d. but with no increase in the proportion of responders, near-maximum pharmacodynamic effect was recorded in tumour biomarker and FDG-PET studies, and dose-limiting toxic effects were present at 200mg.[36]

Choice of comparator: At the time the study was initiated and throughout the enrolment period (December 2010 to September 2011), vemurafenib had not

received regulatory approval so could not be utilised as a comparator. Despite its limited clinical benefit, dacarbazine was considered the standard-of-care for unresectable and metastatic melanoma at the time, and was confirmed as an acceptable comparator through Committee for Medicinal Products for Human (CHMP) Scientific Advice. Patients who progressed on dacarbazine were offered dabrafenib therapy after progression was confirmed by independent review.

Randomisation: Patients were randomly assigned 3:1 to either dabrafenib or dacarbazine; a 3:1 ratio was chosen because it allowed better characterisation of the efficacy and safety of dabrafenib given the small sample dictated by the hypothesised effect size. It was also implemented to mitigate potential concerns around randomisation of patients to a treatment with limited efficacy given emerging clinical data for BRAF inhibitors.

An Independent Review Committee (IRC) was used to review scans to assess response and progression. An Independent Data Monitoring Committee (IDMC) was set up to ensure external objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study.

A CONSORT flow diagram for BREAK-3 is provided in Figure 4.

Supportive RCTs

BRF113220 study[7]

An overview of the study design and methodology of the BRF113220 study is provided in Table 7. Patient enrolment to the study commenced in March 2010. Outcome data presented in this submission are from a planned analysis conducted with a cut-off date of 31 May 2012 and the later cut-off date of 29 March 2013; follow-up is ongoing for overall survival.

MEK115306 Combi-d study[58]

An overview of the study design and methodology of the MEK115306 Combi-d study is provided in Table 7. Patient enrolment to the study commenced in May 2012. Outcome data presented in this submission are from a planned analysis conducted with a cut-off date of 26 August 2013; follow-up is ongoing for overall survival.

Methods

6.3.2 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 7. Comparative summary of methodology of the RCTs

	Primary RCT	Supportive RCTs	
Trial no. (acronym)	**BREAK-3 (BRF113683)** **ClinicalTrials.gov Identifier: NCT01227889**	**BRF113220 (Part C)** **ClinicalTrials.gov Identifier:NCT01726738**	**(Combi-d) MEK115306** **ClinicalTrials.gov Identifier: NCT01584648**
Location	70 centres in 12 countries, including: Germany, France, US, Spain, Italy	Multi-centre study involving 16 centres across the U.S. and Australia	Multi-centre study involving 121 centres across the globe, including centres in the UK
Design	Randomised, open-label, active-treatment controlled, multi-centre phase III study	Randomised, open-label, multi-centre Phase II pivotal study	Randomised, double-blind, multi-centre Phase IIIpivotal study
Population	Subjects with treatment-naïve advanced or metastatic BRAF ^{V600E} mutation-positive melanoma (with the exception of prior treatment with IL-2, surgery or radiotherapy)	Subjects with treatment-naïve metastatic BRAF V600E, V600K or V600D mutation-positive melanoma, with the exception of ≤1 previous chemotherapy regimen and/or interleukin-2 (IL-2)	Subjects with treatment-naïve metastatic BRAF V600E, V600K or V600D mutation-positive melanoma
Duration of study	Ongoing. Enrolment commenced 23 Dec 2010 and completed on 01 Sept 2011. Patients are being followed for overall survival. (latest OS data cut-off; 18 Dec 2012)	Ongoing. Enrolment to Part C commenced 14 December 2010 and the last subject received the first dose of study drug on 07 July 2011. Initial data cut-off; 31 May 2012[7]. Follow-up for OS continues (latest data cut-off; 29 Mar 2013[8]).	Ongoing. Enrolment began in May 2012. The initial data cut was on 26 August 2013 with 211 (50%) PFS events and 95 (22%) OS events. The final analysis of OS is planned when 70% of the total enrolled population has died or been lost to follow up, projected for Q1 2015
Method of randomisation	Upon completion of the required baseline assessments, eligible patients were registered into the GSK interactive voice response system (RAMOS; Registration and Medication Ordering System), by the investigator or authorised study staff, for stratification and central randomisation. Registered patients were assigned a unique subject number for the duration of the study. Subject number and the following baseline subject information for stratification were entered into the system to obtain the treatment assignment: • Disease staging (III + IVM1a + MIVb or IVM1c) Subjects were centrally randomised using a randomisation schedule generated by the GSK Oncology Biometrics Department, which assigned subjects in a 3:1 ratio to receive either dabrafenib or dacarbazine.	Eligible patients were randomised 1:1:1 to receive one of two different dose combinations of dabrafenib plus trametinib, or dabrafenib monotherapy, based on the results from the uncontrolled dose-escalation/expansion cohorts (Part B). In Part C, patients were assigned to study treatment in accordance with the randomisation schedule generated by Discovery Biometrics, using the GSK RAMOS (Registration and Medication Ordering System) interactive voice recognition system (IVRS). Rates of poor prognostic features, such as M1c disease, brain metastases, and elevated lactate dehydrogenase (LDH) levels, were similar between arms in Part C.	Upon completion of all the required screening assessments, eligible subjects will be registered into the Registration and Medication Ordering System (RAMOS), the GSK interactive voice response system (IVRS), by the investigator or authorized site staff. Randomisation was performed on a 1:1 ratio to each arm of the study. The system allowed stratification to the blinded treatment assignment, based upon lactate dehydrogenase levels (LDH; > ULN versus ≤ ULN) and BRAF mutation status (V600E versus V600K).
Method of blinding	This was an open-label study. However, the IRC were blinded to treatment assignment and investigators' assessments of response and progression.	This was an open-label study. Following an interim analysis based on pre-specified Protocol Amendment 3, a Blinded Independent Central Review (BICR) was	Study treatment was double-blinded. Neither GSK, the site, nor the subject will know the treatment assignment. Every

		introduced to evaluate the robustness of the primary analysis, and to support Part C as a potential registration trial for the dual therapy. These analyses were primarily focused on addressing and evaluating potential sources of biases, specifically, with respect to PFS.	effort must be made to maintain the blind until the final PFS analysis is performed.
Intervention(s) and comparator(s)	• Oral dabrafenib 150mg twice daily (n=187) • Intravenous dacarbazine 1000mg/m^2 every 3 weeks (n=63) Dose reductions for dabrafenib and dacarbazine were permitted during study participation, according to dose modification guidelines provided in the study protocol. Patients received treatment until disease progression, death, unacceptable toxicity or study withdrawal. Subjects who experienced disease progression on dacarbazine were eligible for crossover to dabrafenib at the discretion of the investigator following confirmation of progression by independent review.	• Oral dabrafenib 150mg twice daily *plus* trametinib 1mg once daily (150/1), n=54 • Oral dabrafenib 150mg twice daily *plus* trametinib 2mg once daily (150/2), n=54 • Oral dabrafenib 150mg monotherapy twice daily, n=54 Patients who had disease progression on dabrafenib monotherapy could cross over to receive dual therapy 150/2, following confirmation by BICR	• Oral dabrafenib 150mg twice daily *plus* trametinib 1mg once daily (150/1), n=211 • Oral dabrafenib 150mg twice daily *plus* trametinib placebo, n=212 • Crossover was not permitted in this study
Concomitant medication	Subjects received full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. Certain medications were prohibited: including strong inhibitors or inducers or CYP3A or CYP2C8, p-glycoprotein (Pgp) or breast cancer resistance protein (BRCP); St. John's wort; HIV antiretroviral drugs. Concomitant use of certain medications was to be undertaken with caution, particularly: mild/moderate inhibitors and inducers of CYP3A4, CYP2C8, Pgp or BRCP; and substrates of CYP2C8, CYP2C9 and CYP2C19.	Subjects could receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrhoeals, analgesics, and other care, as deemed appropriate. Growth factors and bisphosphonates were allowed but could not be initiated during first 4 weeks of treatment. Certain medications were prohibited while on treatment in this study including: other anti-cancer therapies for melanoma; antiretroviral drugs; herbal remedies (e.g. St. John's wort); therapeutic dosing of warfarin resulting in INR >1.3; strong inhibitors or inducers of CYP3A, CYP2C8, or p-glycoprotein (Pgp) or breast cancer resistance protein (BCRP) transporters as they may alter dabrafenib and/or trametinib metabolism.	Subjects received full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. Use of anticoagulants such as warfarin is permitted provided that INR is monitored in accordance with local institutional practice. Certain medications were prohibited while on treatment in this study including: other anti-cancer therapies for melanoma; antiretroviral drugs; herbal remedies (e.g. St. John's wort); therapeutic dosing of warfarin resulting in INR >1.3; strong inhibitors or inducers of CYP3A, CYP2C8, or p-glycoprotein (Pgp) or breast cancer resistance protein (BCRP) transporters as they may alter dabrafenib and/or trametinib metabolism.
Primary outcomes (including scoring methods and timings of assessments)	*Efficacy:* Progression-free survival (PFS), based on disease assessments by investigators with progression defined according to RECIST v1.1[61]. Tumour assessments involving CT or MRI of chest, abdomen, pelvis, brain, and melanoma skin lesion photography was performed at baseline, week 6, week 12 and every 9 weeks thereafter.	*Efficacy:* • Investigator-assessed progression-free survival (PFS) ○ Disease assessments were conducted at baseline and every 8 weeks, and included imaging (e.g., CT, MRI, bone scan, plain radiograph), and physical examination (as indicated for	*Efficacy:* • Progression-Free Survival (PFS) as assessed by the investigator (assessments conducted from randomization until the earliest date of disease progression (PD) or death due to any cause (average of 9 study months)

		palpable/ superficial lesions). ○ The primary analyses were based on investigators' assessments, with additional analyses conducted according to a blinded independent central review (BICR). Subjects whose disease responded (either CR or PR) had a confirmatory disease assessment performed at least 4 weeks after the date of the assessment at which response was demonstrated. • Overall response rate (ORR: CR + PR) ○ Defined as the percentage of patients achieving either a CR or PR (per RECIST v1.1) [61]. Confirmatory disease assessment was required no less than 28 days after the criteria for response were first met. Exact 95% CI for ORR were calculated. • Duration of response (DoR) ○ Defined (based only on CR or PR) to be the date of first documented evidence of PR or CR until the earlier of date of disease progression or death due to any cause. *Safety:* • Incidence of cutaneous squamous cell carcinoma (cuSCC) • Safety, including AEs, dose modifications and discontinuations, physical/ophthalmical/dermatological examinations, vital signs, ECOG PS, laboratory evaluations, ECG, ECHO All safety analyses were based on the "All Treated" or "Crossover" populations, as appropriate, and were conducted separately for subjects in the randomised phase and those in the crossover phase. AEs were graded according to NCI-CTCAE v4.0. AE	

		assessments were conducted at baseline, throughout the study and 14 days after treatment discontinuation. Where applicable, laboratory data (haematology, chemistry) were graded using CTCAE v4.0.	

Secondary outcomes (including scoring methods and timings of assessments)	*Efficacy*: • PFS as assessed by IRC • Overall survival (OS) • Overall response rate (ORR: CR+PR) • Duration of response • PFS and ORR in crossover patients • Validation of BRAF mutation assay *Health-related quality of life:* • Using EORTC-QLQ-C30 and EQ-5D questionnaires administered at baseline; weeks 6, 12 and 15 during treatment; at progression; and 30 days after progression was first determined. *Safety, included*: • Rate of treatment-emergent non-melanoma skin lesions and second • malignancies • Incidence and severity of adverse events (AEs), graded according to NCI-CTCAE v4.0 • Serious adverse events (SAEs) • Laboratory evaluations (haematology and clinical chemistry) • Physical examinations, vital signs, 12-lead ECG, LVEF • Treatment discontinuations, dose reductions or interruptions Safety assessments were conducted at baseline and every 3 weeks while the subject was on study treatment until 28 days after discontinuation of treatment; exceptions were ECHO and ECG evaluations which were every 9 weeks after week 21 unless clinically indicated, and dermatologic skin examinations (with photography as appropriate) which were every 9 weeks after week 6.	• Overall survival (OS) ○ OS was defined as the interval of time between the date of randomisation/first dose and the date of death due to any cause. For subjects who did not die, OS was censored at the date of last contact. When calculating OS, all deaths following crossover were included. ○ OS was summarized using Kaplan-Meier estimates. For each treatment group, the Kaplan-Meier estimates for median OS and the first and third quartiles are presented, along with 95% CIs. CIs for quartiles were estimated using the Brookmeyer-Crowley method. For the OS comparison of each combination arm with the monotherapy arm, a p-value based on two-sided log rank test was calculated; the Pike estimate of treatment HRs is provided, together with a 95% CI. • Pharmacokinetic (PK) activity Blood was collected for PK analyses pre-dosing on day 15 and every 8 weeks until week 48.	*Efficacy* • OS; defined as the time from randomization until death due to any cause • Overall response rate (ORR), defined as the percentage of subjects with a confirmed CR or PR at any time per RECIST, version 1.1 [Eisenhauer, 2009] • Duration of response, defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among subjects who achieve a confirmed response(i.e.,confirmed CR or PR) *Health-related quality of life:* • Using EORTC-QLQ-C30 and EQ-5D questionnaires administered at baseline; weeks 6, 12 and 15 during treatment; at progression; and 30 days after progression was first determined. *Safety:* The secondary objectives of the study include characterizing the safety profile of dabrafenib and trametinib combination therapy. As a consequence, clinical assessments including vital signs and physical examinations, 12-lead ECG, ECHO, chemistry and haematology laboratory values, and AEs will be monitored and evaluated. *Pharmacokinetic Endpoints* Concentrations of trametinib and of dabrafenib and its metabolites (GSK2285403, GSK2298683, and GSK2167542) will be determined in the combination therapy arm and dabrafenib and its metabolites will be determined in the dabrafenib montherapy arm at each nominal timepoint. As part of the exploratory objectives of this study, the following population PK endpoints will be included:

			• Apparent clearance following oral dosing (CL/F); • Volume of distribution (V/F); and • The effect of combination therapy on CL/F.
Duration of follow-up	All subjects who discontinued study treatment were followed for survival every 12 weeks until death or study completion. Median duration of follow-up (time on study) for dabrafenib and dacarbazine respectively was 5.1 and 4.8 months months at the 19 Dec 2011 data cut; 10.5 and 9.9 months at the 25 June 2012 data cut; and 15.2 and 12.7 months at the 18 Dec 2012 data cut.	All subjects were followed for overall survival every 3 months after last doses of study drugs. Effiacy assessments were made once a pre-specificed endpoint of 70% of PFS events was achieved. • As of the 31 May 2012 data cut-off, median duration of follow-up (time on study) was 14.1 months (range 10.8-17.6) months (70% PFS event rate achieved). All subjects had at least 10 months follow-up. [7] • Median follow-up time at 29 Mar 2013 data cut-off: ~24 months.	Median duration of follow-up (time on study) was approximately 9 months at the 26 August 2013 data cut; Tumour assessments, including radiographic evaluation were made at Week 8 and every 8 weeks thereafter through week 56 and then every 12 weeks thereafter (all ± 7 days) until determination of progressive disease Quality of Life assessments were made at week 8 and every 8 weeks thereafter through week 56 and then every 12 weeks thereafter (all ± 7 days) through determination of progressive disease, and 5 weeks (± 7 days) after determination of progression.

b.d. = twice daily; CR = Complete response; CT = Computed tomography; ECG = Electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D = EuroQol questionnaire; LVEF = Left Ventricular Ejection Fraction; NCI-CTCAE = National Cancer Institute-Common Toxicity Criteria for AEs; PFS = Progression-free survival; PR = Partial response; ORR = Overall response rate; OS = Overall survival; RECIST = Response Evaluation Criteria in Solid Tumours.

Participants

6.3.3 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 8. Eligibility criteria in the RCTs

	Primary RCT	Supportive RCTs	
Trial no. (acronym)	**BREAK-3 (BRF113683)[59]** **ClinicalTrials.gov Identifier: NCT01227889**	**BRF113220 (Part C)[62]** **ClinicalTrials.gov Identifier: NCT01072175**	**(Combi-d) MEK115306[58]** **ClinicalTrials.gov Identifier: NCT01584648**
Main inclusion criteria	• Histologically confirmed advanced (unresectable Stage III) or metastatic (Stage IV) BRAF V600E mutation positive melanoma as determined by central laboratory testing* • Treatment naive for advanced/metastatic disease, with the exception of IL-2, surgery and radiotherapy, which were allowed • Measureable disease according to RECIST v1.[61] • Age ≥18 years. • ECOG PS of 0-1. • Adequate haematological, hepatic, renal and cardiac function.	• Histologically confirmed metastatic BRAF V600E, V600K or V600D mutation-positive melanoma determined locally** • Treatment-naïve for metastatic disease with the exception of ≤chemotherapy regimen and/or IL-2. • Measureable disease according to RECIST version 1.1 [61]. • Age ≥18 years. • ECOG PS of 0-1. • Adequate haematological, hepatic, renal and cardiac function.	• Histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV (metastatic), and determined to be BRAF V600E/K mutation-positive using the bioMerieux (bMx) investigational use only (IUO) THxID BRAF Assay (IDE: G120011). The assay will be conducted by a central reference laboratory*** • Treatment naive for advanced/metastatic disease • Measureable disease according to RECIST v1.1 • ≥ 18 years of age. • An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • Adequate baseline haematological, hepatic, renal and cardiac function

Main exclusion criteria	• Currently receiving anti-cancer therapy or use of any investigational anti-cancer or other drug within 28 days of receipt of first dose of dabrafenib • Major surgery, radiotherapy, or immunotherapy within last 4 weeks • Ocular or primary mucosal melanoma • History of other malignancy. Subjects who had been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma were eligible • History of HIV or G6P dehydrogenase deficiency • Evidence of active CNS disease or cardiac metastases • Cardiac abnormalities, including QTc ≥480 msec; history of acute coronary syndrome (including unstable angina), coronary angioplasty, stenting, or cardiac arrhythmias (except sinus arrhythmia) within the past 24 weeks; NYHA Class II-IV heart failure; or abnormal valve morphology documented by echocardiogram.	• Currently receiving anti-cancer therapy (chemotherapy, radiotherapy, immunotherapy, or biologic therapy) or received an investigational anti-cancer drug within 4 weeks or 5 half-lives of the first dose of study drug administration. • Prior exposure to BRAF or MEK inhibitors. • Known HIV, HBV or HCV infection. • Current use of therapeutic warfarin; use of LMWH was permitted provided PT and PTT met entry criteria. • Any major surgery, radiotherapy, or immunotherapy within the last 4 weeks. Limited radiotherapy within the last 2 weeks. • Evidence of brain metastases; unless all known lesions previously treated with surgery or stereotactic radiosurgery, and confirmed stable, and asymptomatic, and no enzyme-inducing anticonvulsants required. (cases of NED require confirmation on 2 consecutive scans prior to first dose on study). • History of pneumonitis or interstitial lung disease • Cardiac abnormalities including: history of acute coronary syndromes; coronary angioplasty; stenting; QTc interval ≥480 msec; uncontrolled arrhythmias (except controlled atrial fibrillation); NYHA class II-IV heart failure; abnormal cardiac valve morphology; or treatment-refractory hypertension.	• Prior treatment with a BRAF inhibitor (including but not limited to dabrafenib, vemurafenib, LGX818, and XL281/BMS-908662) or a MEK inhibitor (including but not limited to trametinib, AZD6244, and RDEA119). • Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, biologic therapy, or immunotherapy within 21 days prior to randomization, or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to randomization. • History of another malignancy. Exception: Subjects who have been disease-free for 3 years, or subjects with a history of completely resected non-melanoma skin cancer,or subjects with indolent second malignancies are eligible. (Subjects with ocular or mucosal melanoma are not eligible.) • Prior systemic anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy, or investigational treatment) for Stage IIIC (unresectable) or Stage IV (metastatic) melanoma. Prior systemic treatment in the adjuvant setting is allowed. (Note: Ipilimumab treatment must end at least 8 weeks prior to randomization.) • Taken an investigational drug within 28 days or 5 half-lives (minimum 14 days), whichever is shorter, prior to randomization. • 5. Current use of a prohibited medication as described in Table 7 • History of HIV or G6P dehydrogenase deficiency • Evidence of active CNS metastases unless definitively treated with surgery or stereotactic

			surgery or stable for ≥ 12 weeks prior to randomization, and no need for anticonvulsants • Cardiac abnormalities, including QTc ≥480 msec; history of acute coronary syndrome (including unstable angina), coronary angioplasty, stenting, or cardiac arrhythmias (except sinus arrhythmia) within the past 24 weeks; NYHA Class II-IV heart failure; or abnormal valve morphology documented by echocardiogram. • History or current evidence/risk of retinal vein occlusion (RVO) or Central Serous Retinopathy (CSR)

* Screening included central testing for the $BRAF^{V600E}$ mutation performed by the central reference laboratory.
**Archived tissue was required; fresh biopsy was needed if archived tissue was not available. BRAF mutation status was determined locally using GSK BRAF mutation assay.
*** $BRAF^{V600}$ testing was performed using the bioMerieux BRAF THxID IUO assay (IDE: G120011)
ACS = acute coronary syndrome; CNS = central nervous system; CTCAE = Common Toxicity Criteria for AEs ECOG PS = Eastern Cooperative Oncology Group Performance Status; G6PD =glucose-6-phosphate dehydrogenase; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; HIV = human immunodeficiency virus; LMWH = low molecular weight heparin; MI = myocardial infarction; NYHA = New York Heart Association; NED = no evidence of disease; QTcB = QT interval corrected for heart rate using the Bazett's formula.

6.3.4 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.

BREAK-3

The randomised treatment groups in the BREAK-3 study were well balanced for demographic and disease status at baseline (Table 9). All patients were diagnosed with Stage III or IV melanoma.

The majority had M1c disease, which is indicative of a poorer prognosis.[5,19] Approximately half of patients had tumours in at least 3 organs; the most common locations of disease in both arms were lymph nodes, lung, liver and subcutaneous tissue. The dabrafenib group had a slightly greater proportion of patients with metastases in the liver and subcutaneous tissue. All patients were treatment-naïve for metastatic disease (except for one patients who had received interleukin). Most patients had undergone surgery previously and adjuvant immunotherapy (interferon) was the most common prior anti-cancer therapy.

The demographics of patients who eventually crossed over from dacarbazine to dabrafenib in BREAK-3 were consistent with the study population as a whole (Table 9). Subjects who entered the crossover phase as of the data cut-off had more sites of disease compared to subjects entering the randomised phase. The most common locations of disease in the crossover phase were consistent with the randomised phase.

Table 9. Demographic and baseline disease characteristics of participants in BREAK-3 across randomised groups[62]

	Randomised phase		Crossover population (n=28)
	Dabrafenib (n=187)	dacarbazine (n=63)	
Age (years)			
Mean (SD)	53.5 (13.76)	51.6 (14.22)	50.8 (14.39)
Median (Min. – Max.)	53.0 (22-93)	50.0 (21-82)	50.0 (24-75)
Sex, n (%)			
Male	112 (60)	37 (59)	16 (57)
Female	75 (40)	26 (41)	12 (43)
Baseline lactate dehydrogenase, n (%)			
≤ULN	119 (64)	43 (68)	
>ULN	67 (36)	19 (30)	NR
Unknown	1 (<1)	1 (2)	
Prior chemotherapy for advanced or metastatic disease, n (%)			
Any therapy	181 (97)	62 (98)	NR
Surgery	179 (96)	61 (97)	
Immunotherapy	52 (28)	15 (24)	
Radiotherapy	37 (20)	10 (16)	
Biologic Therapy (monoclonal antibodies, vaccines)	3 (2)	3 (5)	
Chemotherapy	1 (<1)	4 (6)	
Hormonal therapy	0	1 (2)	
ECOG PS at Baseline, n (%)			
ECOG =0	124 (66)	44 (70)	NR
ECOG ≥1	62 (33)	16 (25)	
Unknown	1 (<1)	3 (5)	
Stage at screening, n (%)			
IIIC	6 (3)	2 (3)	NR
IV	180 (96)	59 (94)	
TNM staging at screening, n (%)			
M0	6 (3)	1 (2)	NR
M1a	23 (12)	10 (16)	
M1b	34 (18)	12 (19)	
M1c	124 (66)	40 (63)	
Visceral disease at Baseline, n (%)			
No	50 (27)	20 (32)	NR
Yes	22 (12)	8 (13)	
Both	115 (61)	35 (56)	
Number of organs involved, n (%)			
1	42 (22)	19 (30)	3 (11)
2	52 (28)	16 (25)	4 (14)
≥3 sites	93 (50)	28 (44)	21 (75)
Location of disease at baseline, n (%)			
Lymph nodes	120 (64)	38 (60)	20 (71)
Lung	92 (50)	30 (48)	18 (64)
Liver	71 (38)	17 (27)	13 (46)
Subcutaneous tissue	57 (30)	11 (17)	8 (29)
Bone	25 (13)	8 (13)	7 (25)
Spleen	21 (11)	7 (11)	5 (18)
Skin	15 (8)	8 (13)	1 (4)
Adrenal gland	19 (10)	3 (5)	2 (7)
CNS[a]	4 (2)	2 (3)	2 (7)
Other[b]	52 (29)	29 (45)	22 (72)

NR=not reported

a Subjects with CNS metastases were excluded from the randomised phase unless they were without evidence of active CNS metastases for >3 months after surgery or stereotactic radiosurgery.

b Other sites included: muscle, kidney, peritoneum/omentum, mediastinal, ascites, abdomen/abdominalwall

Supportive RCTs

BRF113220 study

The demographics were largely well balanced across the arms of the study. With regards to supporting any efficacy signals that arose from the BREAK-3 study, the demographics of the dabrafenib arm were reasonably well matched between the BRF113220 study and the BREAK-3 study for age, gender, ECOG performance status, and stage of disease at screening. While BREAK-3 comprised of a wholly BRAF V600E mutation populations, the BRF113220 study contained $BRAF^{V600K}$ mutation subjects. However, these subjects were in the minority.

MEK115306 Combi-d study

In a similar manner to the BRF113220 study, the demographics of the MEK115306 Combi-d study were also well balanced across the arms of the study, and contained $BRAF^{V600E/K}$ subjects. Furthermore, the demographics of the subjects within the dabrafenib monotherapy cohort also largely reflected those of the BREAK-3 dabrafenib subject cohort (see Table 10).

Table 10: Comparison of patient characteristics of the dabrafenib monotherapy patient cohorts within the included RCTs

	Primary RCT	Supportive RCT	
Trial no. (acronym)	**BREAK-3 (BRF113683) (n=187)**	**BRF113220 (Part C) Dabrafenib 150mg b.d. Monotherapy (n=54)**	**Combi-d (MEK115306) Dabrafenib 150mg b.d. plus Trametinib placebo (n=212) (n=212)**
Age (years) Mean Median (range)	53.5 53.0 (22-93)	51.8 49.5 (18-82)	55.1 55.0 (22-89)
Sex, n (%) Female Male	75 (40) 112 (60)	25 (46) 29 (54)	100 (47) 111 (53)
ECOG PS, n (%) 0 ≥1	124 (66) 62 (33)	34 (63) 20 (37)	54 (26) 155 (73)
Stage at screening, n (%) IIIc IV	6 (3) 180 (96)	1 (2) 53 (98)	5 (2) 206 (98)

TNM staging at screening, n (%) M0 M1a M1b M1c	6 (3) 23 (12) 34 (18) 124 (66)	1 (2) 11 (20) 5 (9) 37 (69)	- 19 (9) 45 (21) 142 (67)
LDH level at baseline, n (%) Elevated (>ULN) Normal (≤ULN)	37 (36) 119 (64)	27 (50) 27 (50)	76 (36) 135 (64)
No. of organs involved, n (%) <3 sites ≥3 sites	94 (50) 93 (50)	34 (63) 20 (37)	109 (52) 101 (48)

Outcomes

6.3.5 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 (HRQoL), 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.

Details of the primary and secondary endpoint measures in BREAK-3, are presented in Table 11**.** The outcomes of the BRF113220 study and the MEK115306 Combi-d study largely reflect those found within the BREAK-3 study, although there are some differences with regard to whether the outcomes are classed as primary or secondary measures.

Table 11. Primary and secondary outcomes of the RCTs

BREAK-3 (BRF113683)	
Primary outcomes and measures	**Reliability/validity/current use in clinical practice**
• Progression-free survival (PFS) in the entire study population, as assessed by investigators according to RECIST v1.1 criteria (see below) [61] • PFS was defined as the interval between the date of randomisation and the earliest date of objective disease progression or death due to any cause **RECIST Criteria v1.1 for evaluation of target lesions*:** • *Complete response (CR)* – Disappearance of all target lesions • *Partial response (PR)* – At least a 30% decrease in the sum of the LD of target lesions, taking as a reference the baseline sum LD • *Progressive disease (PD)* – At least a 20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions • *Stable disease (SD)* – Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since treatment started • *Not evaluable (NE)* – Any subject who cannot be classified by one of the four preceding definitions. PFS was also examined in pre-defined sub-groups including: • Gender • No. of metastatic disease sites (<3 or ≥3) • Age (<65 or ≥ 65 years) • Disease stage at screening (IIIc + IVM1a+ IV1Mb or IVM1c) • ECOG PS (0 or ≥1)	PFS has not been widely acknowledged as a surrogate endpoint for OS in advanced or metatstatic melanoma specifically [5], although it is widely recognised by oncologists and regulatory authorities as an important endpoint and a valid measure of clinical benefit in advanced-stage cancer trials[59,60] . Data for molecular targeted agents against BRAF V600 mutated-melanoma suggest that a large benefit in PFS is likely to correlate with improved OS [32]. Due to ethical requirements in clinical trials, it is necessary to allow subjects to crossover from the comparator arm to receive the treatment within the active arm of the study; in allowing this, this does not deprive subjects of receiving the potentially more effective treatment from the active arm of the study. It is therefore also widely regarded that, due to the confounding effect of crossover on OS, it is difficult the estimate the true survival beneft in this setting. PFS was therefore selected as the most appropriate primary endpoint since its effects are not diluted by post-progression treatment following crossover. Data for molecular targeted agents against BRAF V600 mutated-melanoma suggest that a large benefit in PFS is likely to correlate with improved OS. A meta-analysis of randomised, controlled trials in metastatic melanoma demonstrated that PFS may be used as a surrogate for OS. [63] This analysis used OS and PFS as defined and reported in selected trials following a systematic review of the literature. Results demonstrated a strong correlation between treatment effects on PFS and OS. A sensitivity analysis to account for the limitations in measuring the true treatment effect for OS in studies with crossover was also performed, and also showed a very strong correlation between the treatment effects on PFS and OS. (See Appendix **Error! Reference source not found.** for further details) PFS is a composite endpoint that informs on both tumour response/shrinkage and disease stabilisation. Furthermore, PFS is a direct measure of treatment effect and not subject to the influence of crossover/post-study therapy and is therefore particularly acceptable in situations where it is expected that further lines of treatment may hamper the detection of a treatment effect on OS.[60] Progression-free survival is an important health outcome in its own right as it measures only the effect of the study drug and is not diluted by subsequent treatments which patients receive, as OS may be. Expert medical opinion considers that, as disease progression is often symptomatic and uncomfortable, an improvement in PFS is beneficial to patients in-and-of itself in lethal diseases such as late-stage MM, if the magnitude of the benefit is sufficient and the side-effect profile acceptable. Progression was determined by the investigator using the internationally-recognised and widely

	used Response Evaluation Criteria In Solid Tumours (RECIST) [57] (see left-hand column) based on imaging data (including photography). Sensitivity analyses are recommended for a rigorous assessment of PFS [61,62]. Several sensitivity analyses of PFS using the ITT population were conducted to confirm the results of the primary analysis, including: investigator-determined symptomatic progression as a PFS event; PFS censoring at date of last scan for subjects with no PFS event at cut-off; Cox regression analysis using baseline prognostic factors as covariates. An independent central reviewer, who was blinded to the treatment assignment, performed a blinded, retrospective evaluation of progression. The progression dates from this review were used to perform a secondary analysis of PFS.
Secondary outcomes and measures	**Reliability/validity/ current use in clinical practice**
Principal secondary endpoint: • Overall survival (OS) – defined as the interval between date of randomisation and date of death due to any cause. *Other secondary endpoints included:* • Overall response rate (ORR) – defined as the percentage of patients achieving either a confirmed CR or PR as per RECIST criteria v1.1 as their best overall response • Duration of response (DoR) – defined as the time for those subjects who show a CR or PR from the first documented evidence of CR or PR until the first documented sign of progression or death due to any cause • PFS2 – defined as the time from first dose of dabrafenib in subjects randomised to dacarbazine who crossover after initial progression	OS is considered the gold standard measure of clinical benefit and the most objective endpoint [59,60] in phase III RCTs of cancer therapies. It is generally required by regulatory agencies to be a key secondary endpoint where PFS is the primary endpoint[59]. However, OS is frequently confounded by crossover or other therapies received by patients upon discontinuation of study medication following disease progression. Because BREAK-3 permitted subjects randomised to dacarbazine to receive dabrafenib after progression, the survival times of these crossover subjects was expected to be longer than what would have been observed without crossover. The Reporting and Analysis Plan (RAP) therefore allowed for analyses to be conducted to examine and adjust for the impact of crossover, including the Rank Preserving Structural Failure Time (RPSFT) model.[64] ORR is considered to be an appropriate and valid secondary endpoint in the phase III evaluation of some new anti-cancer treatments and/or in some cancers, including melanoma.[65] However, melanoma experts maintain that response rates can under- or over-estimate an agent's effects; for example, high initial response rates with some therapies have not translated into an OS benefit whereas low response rates with ipilumumab, for example, have translated into an OS benefit.[65] Tumour response evaluations were made using the established Response Evaluation Criteria In Solid Tumours (RECIST v1.1) [57] (see above). Separate response analyses were performed using the investigators' and independent reviewer's assessment of response.

to the earliest date of documented progression or death • ORR and DoR in subjects who crossover to dabrafenib after initial progression on dacarbazine	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.
Health outcomes assessments: • EQ-5D (EuroQoL-5D questionnaire) • EORTC-QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3)	Although several melanoma instruments were in development, there were no widely used, uniformly accepted, and fully-validated disease-specific instruments at the time this study was set up. Generic instruments for assessment of health-related quality of life (HRQoL) were therefore used in this study. The EQ-5D was included in this study as a standardised measure of health status that is applicable to a wide range of health conditions. It has been shown to be reliable and valid for assessing health-related QoL in cancer patients. It comprises a 5-item health status measure (index) which is used to calculate a utility value and a visual analogue rating scale (VAS/thermometer; rated 0 to 100) to rate overall health[66]. The EQ-5D was therefore included in this study as a standardised and validated instrument considered to be relevant in the assessment of HRQoL in subjects with RCC (Cella 2009). It comprises a visual analogue rating scale (VAS; rated 0 to 100) and a 5-item health status measure[66]. The EORTC-QLQ-C30 is a self-reporting 30-item cancer specific instrument that includes measures of physical, role, emotional, cognitive and social functioning [67]. Scoring of the QLQ in this study was based on published methods that transformed all scales to scores between 0 and 100[68] The EORTC QLQ-C30 has been validated in over 60 languages and been shown to be highly consistent across different language/cultural groups[67,69]. The instrument has also been shown to be responsive to change and all scales/single items meet the standards for reliability.
Safety assessments: • Adverse events (AE) – collected and recorded from first dose of study treatment until 28 days following discontinuation of study treatment • Serious adverse events (SAE) – collected over same time period • Rates of treatment-emergent non-melanoma skin lesions and second malignancies	AEs were coded using the industry standard dictionary for regulatory activities (MedDRA) and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) (version 4.0), a descriptive terminology that is well accepted and widely used for recording (grading) the severity of adverse events. Serious adverse events were defined according to the Good Clinical Practice Guideline (see section 6.9). Investigators or site staffs were responsible for the detection and documentation of events meeting the criteria/definition of an AE and SAE and for judging whether or not they were related to study drug. Details of adverse events (including frequency and severity) experienced by patients receiving treatment for metastatic melanoma would be recorded routinely in clinical practice.

• Treatment discontinuations, interruptions or dose modifications (all and due to AEs)
 	
• Clinical laboratory tests including:
  ○ Clinical chemistry including: sodium, potassium, phosphate, magnesium, creatinine, bilirubin, AST, ALT, ALP, γ-GT, glucose, LDH, amylase, lipase, cardiac troponin
  ○ Haematology including: haemoglobulin, RBCs, WBCs, neutrophils, lymphocytes, platelets
  ○ Urinalysis
• Vital signs
 	
• Physical and dermatology examinations
 	
• 12-Lead ECG
 	
• LVEF (assessed by echocardiogram)
 	
• WHO PS
	Any abnormal laboratory test results (clinical chemistry, haematology, urinalysis) or other safety assessments /events (e.g. ECG, vital sign measurements) felt to be clinically significant in the judgement of the investigator were recorded as an AE or SAE in accordance with the protocol definitions provided. Laboratory safety data were flagged high or low relative to the normal range and were graded programmatically according to the CTCAE v4.0
	
	Frequent biochemistry and haematology assessments are performed in patients with metastatic melanoma in clinical practice and it is standard to compare results with reference ranges.
	
	Assessment of vital signs and physical examination are routine clinical procedures.
	
	Baseline and regular ECG and/or LVEF assessments would be conducted as part of the routine clinical management of patients with advanced/metastatic STS, especially those who have received prior anthracycline-based therapy.
	
	WHO PS is a reliable, widely accepted and widely used method (5-point scale) of assessing the functional status and ability to self-care of cancer patients and used to assess patients' performance status in clinical practice.

Exploratory Assessments • BRAF Mutation in Circulating Cell Free-DNA Circulating cell free-deoxyribonucleic acid (cfDNA) from patient plasma samples will be explored to determine whether BRAF mutations in cfDNA correlate with mutations in the same patient's tumor tissue. from which it is derived. Additionally cfDNA may be evaluated for other mutations associated with response to GSK2118436 at baseline and on progression of disease. The analysis will investigate additional potential predictive biomarkers of treatment response or will allow investigation of intrinsic and/or acquired markers of resistance. Details on the assessment of BRAF mutations in cfDNA are provided in Section 6.7. • Tumor Biomarker Analysis Optional tumor biopsies willmay be obtained for exploratory biomarker analyses. . The analyses will investigate additional	These exploratory assessments are not used in routine clinical practice. However as part of translational research, they may be used to evaluate responses to the intervention treatment.

potential predictive biomarkers to treatment response and/or response or will allow investigation of intrinsic or acquired markers of resistance. • Pharmacogenetics (PGx) Research Objective To investigate the relationship between genetic variants in host DNA and the pharmacokinetics of GSK2118436 and/or the relationship between genetic variants in host DNA and the efficacy, safety and tolerability of GSK2118436.	

Statistical analysis and definition of study groups

6.3.6 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.

Primary hypotheses and statistical analyses undertaken for BREAK-3 are described in Table 16 below. Comprehensive statistical plans were also devised for the BRF113220 study and the MEK115306 Combi-d study. These have been included within Appendix 10.12 for completeness.

Table 12. Summary of statistical analyses in BREAK-3 (BRF113683)

Hypothesis objective	Sample size, power calculation	Statistical analyses, analysis populations	Data management, patient withdrawals
The primary objective was to evaluate and compare PFS in subjects treated with dabrafenib compared with those treated with dacarbazine. The study was designed to provide evidence to support the null hypothesis H0: λ ≥ 1 or to reject it in favour of the alternative hypothesis HA: λ < 1, where λ is the hazard ratio for PFS for dabrafenib relative to dacarbazine.	Target enrolment and event requirements were defined to achieve statistical power of 99.7% to detect a 67% reduction in risk of progression or death (corresponding to a hazard ratio [HR] of 0.33) in subjects who received dabrafenib (median PFS of 6 months) compared with subjects who received dacarbazine (median PFS of 2 months), equating to a 200% improvement in median PFS. At least 200 patients were to be enrolled to observe a minimum of 102 PFS events required for the first analysis of PFS.	The *Intention-to-treat (ITT) Pop*ulation, which comprised all randomised patients, was used for analyses of the efficacy data based on the treatment to which the subject was randomised. Safety data were analysed using the *Safety Population*, which was defined as all randomised subjects who received at least one dose of study medication and was based on the actual treatment received if that differed from that to which the subject had been randomised. The *Crossover Population* comprised the subset of subjects who were randomized to the dacarbazine arm and who elected to cross over to receive dabrafenib after progression was confirmed. *Efficacy analyses:* PFS and OS were estimated using Kaplan-Meier curves, and compared between treatment arms using a log-rank test stratified on disease staging. The Pike estimator[63] of the treatment HR was provided, together with a two-sided 95% confidence interval (CI). The primary analysis of PFS was conducted using progression dates as determined by investigators; an analysis was repeated using dates from the independent review. Updated efficacy analyses were conducted at later time points. Sensitivity analyses of PFS were conducted to confirm the results of the primary analysis including: investigator-determined symptomatic progression as a PFS event; PFS censoring at date of last scan for subjects with no PFS event at cut-off; Cox regression analysis using baseline prognostic factors as covariates. A sensitivity analysis of OS using the latter method was also performed. Response rates were compared between randomised treatment arms using a Fisher's exact test. An exact 95% CI for the difference in response rates between randomized treatment arms was calculated. ORR (defined as subjects achieving a CR or PR per RECIST v1.1) end was calculated from both the investigators' and the independent reviewer's assessment of response. Median duration of response (DoR) was calculated from the Kaplan-Meier estimates for subjects in the ITT population who showed a CR or PR. PFS, OS, ORR and DoR were analysed separately for the ITT and Crossover Populations.	*Treatment discontinuation*: Subjects received study treatment until disease progression, death or unacceptable toxicity. Subjects could also withdraw from the study for other reasons. All subjects who withdrew were included in analyses up to the time of withdrawal, regardless of treatment duration. All subjects who permanently discontinued study treatment without disease progression were followed for progression until progression, start of new anti-cancer therapy, or death. Subjects are being followed-up until death; however, once 70% of the enrolled subjects have died or been lost to follow-up the collection of survival follow-up data for subjects who have discontinued treatment will cease and the study will be closed for further follow-up. *Withdrawals*: A subject will be considered to have withdrawn from the study if the subject has not died and is lost to follow-up, has withdrawn consent, is no longer being followed at the investigator's discretion, or if the study is closed or terminated. A subject will be considered to have completed the study if the subject dies during the study treatment or follow-up period. *Missing data*: All available time-to-event data were analysed using suitable statistical methods; patients with shorter treatment and follow-up due to the natural history of their disease or medical necessities of the treatment of their disease will not be considered to have missing time-to-event data. There was no imputation for missing data. Subjects with unknown or missing best overall response were assumed to be non-responders, and included in the denominator when calculating percentages. *Censoring*: PFS: Subjects with a progression event after an extended loss to follow-up time were censored at the date of the last adequate assessment prior to loss to follow-up. Additionally subjects who started a new anticancer therapy prior to the progression event were censored at the last adequate assessment prior to the

		Safety analyses: Adverse events (AEs) were summarised by frequency/proportion of total subjects using descriptive techniques only. AEs were graded by investigators according to the NCI CTCAE v4.0. Separate summaries were provided for all AEs, drug-related AEs, serious AEs (SAEs), and AEs leading to discontinuation/dose reduction/treatment interruption. AEs of special interest were also summarised. In particular, the rate of non-melanoma skin lesions and the rate of other malignancies was calculated as the percentage of subjects with the appearance of any treatment-emergent non-melanoma skin lesions/other malignancy after the start of treatment. Exact 95% confidence intervals were calculated for each. Clinical chemistry and haematology data were summarised according to NCI CTCAE grade (version 4.0).The maximum toxicity grade of a laboratory parameter for a subject was the worst grade post-baseline after the first dose of study treatment over the treatment period. Any grade increases and specific increases to Grade 1, Grade 2, Grade 3, and Grade 4 were summarised. Safety data were handled separately for the randomised and crossover phases. *Health-related quality of life (HRQoL) analyses:* The HRQoL endpoint was change from baseline in HRQoL, based on patient self-reported scores collected using the EORTC QLQ-C30 version 3 and the EQ-5D questionnaires. The analyses for EORTC-QLQ-C30 were focussed on the Global Health Status/QoL score and the analyses for the EQ-5D were focussed on the EQ-5D Index and EQ-5D Visual Analogue Scale (VAS). A mixed-model repeated measures analysis of covariance (ANOVA) was used using baseline scores as a covariate.	start of new therapy. Subjects who had not progressed or died at the time of analysis were censored at the last adequate assessment. OS: Censoring was performed using the date of last known contact for those who were alive at the time of analysis

Statistical methodology to adjust for confounding due to treatment switching

In the BREAK-3 study, patients randomised to the control arm were permitted to receive the investigational treatment, dabrafenib monotherapy upon initial disease progression. This was also allowed in the BRF113220 study, where patients receiving the dabrafenib monotherapy were allowed to receive the combination of the dabrafenib and trametinib, upon independently confirmed disease progression. The MEK115306 Combi-d study did not allow patients to crossover from the dabrafenib arm to the arm which received the combination of dabrafenib (150mg) and trametinib (2mg). Table 13 below presents the proportion of patients whom crossed over in this way in the studies that are relevant to this decision problem.

Table 13: Level of patient crossover at different data points for BREAK-3 and BRF113220

	BREAK-3			BRF113220 study (150/2 arm)	
Datacut (date)	Dec 2011	Jun 2012	Dec 2012	May 2012	Mar 2013
% control group crossing over on progression (%)	44	56	57	80	83

Where crossover occurs, ITT analyses may underestimate the incremental benefit of treatment because they do not account for the fact that patients in the control arm are likely to perform better having crossed over to receive the experimental treatment than they may have done had they not been afforded this opportunity. If crossover occurs at the time of disease progression, as is the case with BREAK-3 and BRF113220, it is the OS result that is impacted.

The optimal method to adjust for the confounding effect of crossover in survival analyses in RCTs remains an area of academic debate and all approaches have their strengths and limitations. Several approaches were applied to these datasets to evaluate the impact of crossover on the OS data from BREAK-3 and BRF113220.

Naive methods

- Censoring crossover patients at the time they crossover

  In this analysis, patients who crossover from control arm to intervention are censored at the date of crossover. OS for other subjects is measured from the time of randomisation to death or last contact.

- Excluding crossover patients from the OS analyses

- Cox regression with crossover as a time-dependent covariate

  Patients are modelled in one of two states over time: the first representing the control arm to which they were randomised, the second representing crossover to experimental treatment. Until crossover for patients in the control arm, the hazard relates to control therapy while from the time of crossover to the experimental arm, the hazard relates to experimental treatment.

These simple/naïve methods are highly prone to selection bias because treatment crossover is likely to be associated with prognosis.[64] When patients who cross over are censored or excluded from the analysis, or when treatment is included as a time-dependent covariate, the randomisation balance between groups is broken if crossover is associated with prognostic patient characteristics. These methods are explicitly not recommended by NICE.[65]

Complex methods

- Rank Preserving Structural Failure Time Model (RPSFT)

  RPSFT uses a counterfactual framework to estimate the causal effect of treatment based upon trial randomisation, i.e. this method estimates the difference in OS between treatment groups assuming that patients on control had not crossed over to the experimental arm and remained on the control drug for the duration of the study. In order to achieve this, the method separates the observed event time (Ti) for each patient into two; the event time when the patient is on the control treatment (TAi), and the event time when the patient is on the intervention treatment (TBi). For patients who are randomised and who do not switch treatment, i.e. full compliance, TAi is equal to zero. However, for patients who switch treatments (for whom compliance is imperfect) both TAi and TBi will be greater than zero. Since the RPSFT method is based on the ITT population, it avoids potential pitfalls and biases that adjust for post-randomsiation time-dependent covariates and, instead, maintains the original randomised group definitions. RPSFT therefore preserves the validity of between group comparions and is said to produce "randomisation-based effect estimators".[66]

  The RPSFT method relates Ti to the counterfactual event time (Ui) with the following causal model:

  $$Ui = TAi + e^{\varphi 0} TBi$$

  Thus time spent on the control treatment, and time spent on post-study therapy, are combined to represent time "off" treatment. This methodology has been applied in several recent NICE appraisals, [40,67-71] including the recent assessment of vemurafenib – the key comparator in this decision problem.

- Iterative Parameter Estimation (IPE)

  The IPE is an extension of the RPSFT method using parametric methods. This uses the same accelerated failure time model but fits a parametric failure time model (e.g. Weibull, log logistic, lognormal) to the original, unadjusted ITT data to obtain an initial estimate of φ and the counterfactual survival time model presented in the above equation. The treatment groups are then compared again using the parametric model to give an updated estimate of φ. The process of re-estimating the observed survival times of crossover patients is repeated in an iterative process until the new estimate for e^{φ} is very close to the previous estimate at which point the process is said to have converged. As with the RPSFT method, the significance level remains the same as that associated with the ITT analysis.

  The IPE method produces very low levels of bias when the assumptions made by the method (in particular, the "common treatment effect" assumption) hold.[64,66,72] Morden et al (2011) and Latimer et al (2012) found that the method's performance was very similar to the RPSFT, which is to be expected as the methods are similar other than in their estimation procedure.

- Inverse Probability of Censoring Weighting (IPCW) analysis

  This method aims to adjust for crossover by recreating the population that would have been evaluated had crossover not occurred. Therefore, those subjects who do not cross over get a greater weighting in order to correct for the resulting bias.

Alternative applications of the RPSFT and IPE methods can be tested – see below.

Alternative applications of the RPSFTM and IPE methods

In applying the RPSFTM and IPE methods to a dataset, different assumptions can be made relating to the continuation of the treatment effect after treatment discontinuation.

- On treatment analysis: In this approach, crossover is accounted for not only from the control group to the experimental treatment, but also from experimental treatment to the control group. This results in a "causal" treatment effect being estimated for the experimental treatment – that is, the effect while on treatment. Essentially this provides an estimate of the treatment effect of full treatment (with no discontinuation) compared to no treatment and it assumes that the treatment effect is lost as soon as treatment is discontinued.
- On treatment - observed analysis: Uses the "on treatment" analysis in order to derive counterfactual survival times for the control group. Then, rather than comparing these to counterfactual survival times for a fully treated experimental group, these are compared to the observed experimental group survival times. This provides an estimate of the treatment effect that has more meaning, and which is applicable to the entire experimental group across all time periods in the economic model.
- Treatment group analysis: This analysis assumes that there is no crossover from the experimental treatment onto the control treatment and once treatment has begun the patient remains in the "treated" group. This approach estimates the average effect of being randomised to the experimental group compared to the control group over the entire observed lifetimes of patients – it does not require that the treatment effect stops upon treatment discontinuation.

The treatment group approach was deemed appropriate for all trials because it provides a longer period of follow-up for dabrafenib OS (due to less re-censoring). Results from this and all other analyses are provided in Table 26.

Adjustment of the GSK trial data for the confounding effects of crossover were conducted by Nick Latimer at the School of Health and Related Research (ScHARR), University of Sheffield on behalf of GSK (reports available upon request).[60] An extensive assessment of which methods would be most appropriate for the GSK datasets was undertaken by ScHARR and full technical details regarding the application of these methods are available upon request. The Inverse probability of censoring weighted (IPCW) analysis – an observational method which effectively recreates the population that would have been evaluated if crossover had not occured – was not deemed appropriate for these datasets. This was due to paucity of data from the trials. In particular there was very little data on control patients who died without crossing over. These are an important group in an IPCW analysis because they are used to form a 'pseudo' weighted population based upon baseline and time-dependent covariates. When very few events are observed in this group, the method is unlikely to provide robust results.[72] GSK intends to run IPCW adjustments on the mature datasets from these trials if this is advised in future by ScHARR.

In summary, the treatment-group RPSFT method was deemed most appropriate for the data-sets used and sample size being evaluated in the economic modelling, and was therefore selected as the preferred adjustment method in this appraisal.

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

BREAK-3[5,59]

The following pre-specified subgroups were explored in the analysis of selected efficacy endpoints as these are recognised prognostic factors[19,73-75] in metastatic melanoma:

- Gender (male *or* female)
- ECOG performance status at baseline (0 *or* ≥1)
- Age (<65 years *or* ≥65 years)
- Lactate dehydrogenase levels (≤ULN *or* >ULN)
- Disease stage at baseline (IIIc, IVM1a, IVM1b *or* IVM1c)
- Number of disease sites at baseline(<3 *or* ≥3)

Tests for interaction have been supplied as supplementary evidence.

Participant flow

6.3.8 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 BREAK-3

A total of 250 patients with $BRAF^{V600}$ mutation-positive metastatic were randomised to receive dabrafenib (n=187) or dacarbazine (n=63).[5] Patient disposition at the cut-off date (19 December 2011) for the first PFS analysis (requiring 102 investigated-assessed events) is summarised in Table 14 and presented as a CONSORT flow diagram in Figure 4. The consideration of crossover has been covered in section 6.3.6.1. Patient disposition at later cut-offs for updated efficacy and safety analyses are shown in Table 15 and Table 16.

Table 14. Summary of patient disposition (BREAK-3, ITT population, 19 December 2011 cut-off)[59]

	Randomised phase		Crossover group N=28
	Dabrafenib N=187 n (%)	dacarbazine N=63 n (%)	
Subjects			
Died	21 (11)	9 (14)	-
Treatment Status			
Ongoing (still on study treatment)	107 (57)	17 (27)[b]	21 (75)
Discontinued study treatment	80 (43)	46 (73)	7 (25)
Primary reason for Treatment Discontinuation[a]			
Disease progression	66 (35)	43 (68)	6 (21)
Adverse event	5 (3)	0	0
Investigator discretion	4 (2)	2 (3)	1 (4)
Decision by subject or proxy	5 (3)	1 (2)	0

a. Subjects had only 1 primary reason for treatment discontinuation
b. n=63 included in ITT population; n=59 included in safety population who took at least 1 dose of study medication, therefore 3 patients not included in safety population: n=14 still on study treatment by data cut-off

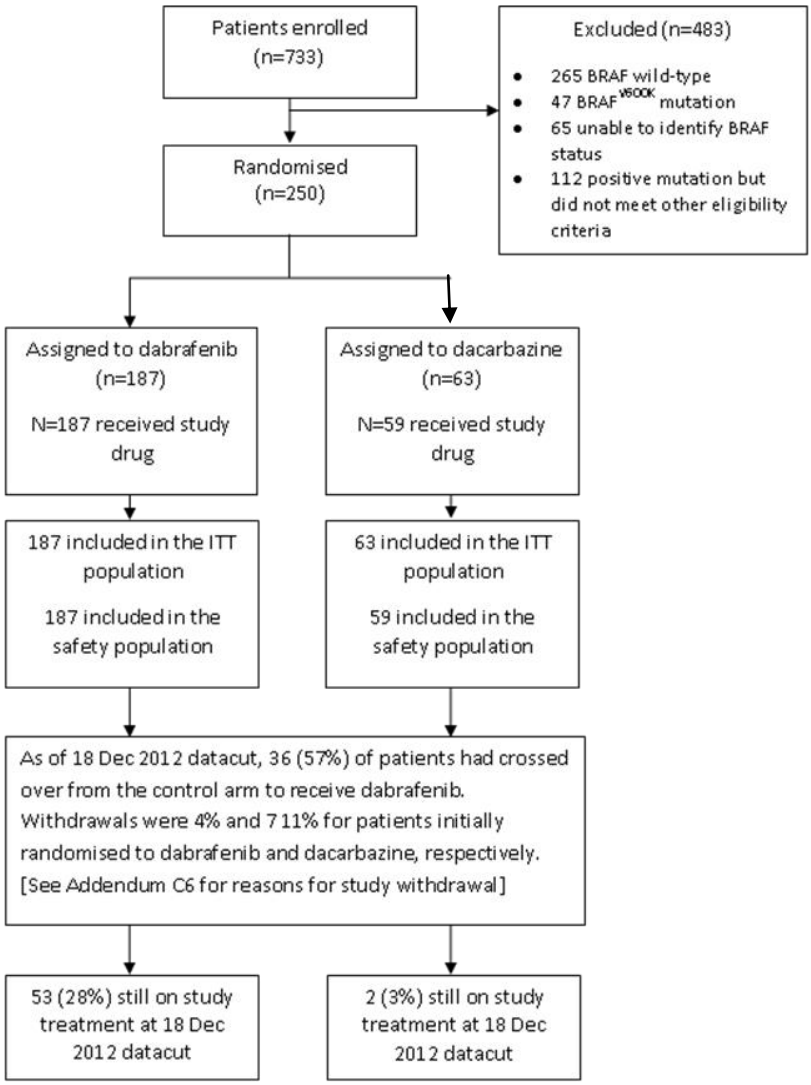


Figure 4. CONSORT diagram (BREAK-3, December 2012 cut-off)

Table 15. Summary of patient disposition (BREAK-3, ITT population, 25 June 2012 cut-off)[6]

	Randomised phase[b]	
	Dabrafenib N=187 n (%)	dacarbazine N=63 n (%)
Subjects		
Died	55 (29)	21 (33)
Treatment Status		
Ongoing (still on study treatment)	71 (38)	5 (8)
Discontinued study treatment	116 (62)	54 (92)
Primary reason for Treatment Discontinuation[a]		
Disease progression	97 (52)	47 (80)
Adverse event	6 (3)[b]	0
Investigator discretion	7 (4)	4 (7)
Decision by subject or proxy	6 (3)	3 (5)

a. Subjects had only 1 primary reason for treatment discontinuation

b. Patient disposition in crossover group at 25 June 2012 data cut-off not available at the time of this report

Table 16. Number of deaths at latest cut-off (BREAK-3, ITT population, 18 December 2012 cut-off)[6]

	Randomised phase[b]	
	Dabrafenib N=187 n (%)	dacarbazine N=63 n (%)
Subjects		
Died[a]	78 (42)	28 (44)

a. Median duration of follow-up: 15 months – patients alive: dabrafenib 63%, dacarbazine 51%

b. Deaths in crossover group at 18 December 2012 data cut-off not available at the time of this report

Patient disposition in BRF113220 (Part C)

A total of 162 subjects with BRAF mutation-positive stage IIIc or stage IV melanoma were enrolled in BRF113220, Part C; 54 patients were randomised to each treatment arm.[7] Subject disposition at the cut-off date (31 May 2012) for the PFS analysis is summarised in Table 17. It is difficult to compare across these trials in terms of subject status. Around 60% of subjects were ongoing in the BRF113220 study, either on treatment or in the follow-up period at the first data cut-off (31 May 2012). This mirrored the findings in the BREAK-3 study. As would be expected, as follow-up continued, more subjects would experience disease progression or die. Since crossover was allowed upon confirmed disease progression, around 80% of subjects receiving dabrafenib monotherapy were allowed to crossover to the the treatment arm which received the combination of dabrafenib (150mg) and trametinib (2mg) at the first data cut-off (31 May 2012).

Table 17. Summary of subject disposition (BRF113220 Part C, ITT population, 31 May 2012 cut-off)[62]

	Dabrafenib Monotherapy 150mg b.d. N=54	Dabrafenib 150mg b.d. *plus* trametinib 1mg o.d. N=54	Dabrafenib 150mg b.d. *plus* trametinib 2mg o.d. N=54	Total (All Dose Groups)
Subject Status, n (%)				
Died	19 (35)	18 (33)	14 (26)	51 (31)
Ongoing in study	35 (65)	32 (59)	40 (74)	107 (66)
On study treatment	16 (30)	23 (43)	23 (43)	62 (38)
In follow-up	19 (35)	9 (17)	17 (31)	45 (28)
Withdrawn from study	0	4 (7)	0	4 (2)
Primary Reason for Study Withdrawal[a], n (%)				
Withdrew consent	0	4 (7)	0	4 (2)

Note: Monotherapy group includes data from the crossover phase.
a. Subjects may have only one primary reason for withdrawal

Table 18 summarises study treatment status. (Note that one subject originally randomised to the dabrafenib monotherapy group inadvertently received the dual (150/2) therapy and is therefore included in this group).

Table 18. Summary of treatment status (BRF113220 Part C, All treated population, 31 May 2012 cut-off)[62]

	Dabrafenib Monotherapy 150mg b.d. N=53[a]	Dabrafenib 150mg b.d. *plus* trametinib 1mg o.d. N=54	Dabrafenib 150mg b.d. *plus* trametinib 2mg o.d. N=55[a]	Total (All Dose Groups) N=162
Treatment Status, n (%)				
Ongoing	3 (6)	23 (43)	23 (42)	49 (30)
Crossed-over	43 (81)	0	0	43 (27)
Discontinued	7 (13)	31 (57)	32 (58)	70 (43)
Primary[b]/Subreason for Treatment Discontinuation, n (%)				
Lack of efficacy	5 (9)	26 (48)	25 (45)	56 (35)
Disease progression	5 (9)	26 (48)	25 (45)	56 (35)
AE	1 (2)	3 (6)	7 (13)	11 (7)
Subject or proxy decision	1 (2)	2 (4)	0	3 (2)
Other	1 (2)	2 (4)	0	3 (2)

a. One subject was randomised to receive dabrafenib monotherapy but instead received 150/2 dual therapy, and is therefore included in the 150/2 dual therapy group (having received this treatment) rather than the monotherapy group.
b. Subjects may have only one primary reason for discontinuation.

Table 19 below provides a summary of treatment status following the latest data cut-off from BRF113220 of 29 March 2013, which included the updated, post-hoc OS analysis.

Table 19. Summary of treatment status (BRF113220 Part C, All treated population, 29 March 2013 cut-off)[8]

Subject Status, n (%)	Dabrafenib Monotherapy 150mg b.d. N=53[b]	Dabrafenib 150mg b.d. *plus* trametinib 1mg o.d. N=54	Dabrafenib 150mg b.d. *plus* trametinib 2mg o.d. N=55[b]	Total (All Dose Groups) N=162
Duration of treatment (randomised phase)[a]				
≤ 6 months	26 (48)	16 (30)	14 (25)	56 (35%)
6-12 months	23 (43)	12 (22)	17 (31)	52 (32%)
> 12 months	4 (7)	26 (48)	24 (44)	54 (33%)
Overall study status				
Death	31 (57)	27 (50)	25 (46)	
Ongoing on study treatment	9 (17)[b]	14 (26)	18 (33)	41 (25%)

a. Duration of treatment data for monotherapy dabrafenib includes exposure prior to crossover only
b. 1 patient on randomised dabrafenib monotherapy; 8 patients on 150/2 crossover treatment

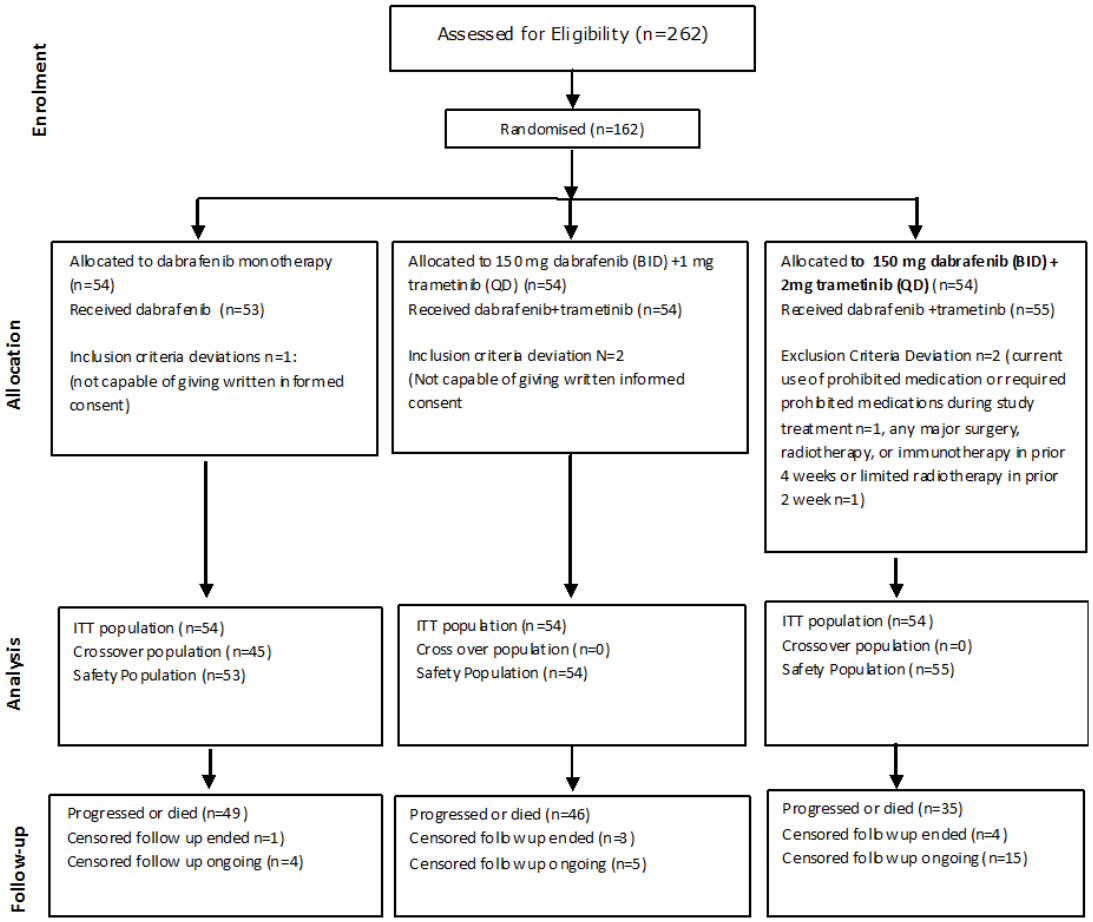


Figure 5. CONSORT diagram. BRF113220 (Part C; 31 May 2012 cut-off)

Patient disposition in the MEK115306 Combi-d study

Subjects enrolled in MEK115306 adequately represent the first-line patient population of $BRAF^{V600E}$ and $BRAF^{V600K}$ mutation-positive, unresectable and metastatic melanoma. At the time of data cut-off (26 Aug 2013), death had occurred in 19% of subjects in the combination arm and 26% of subjects in the monotherapy arm. Approximately two-thirds of subjects were still ongoing in the study. As has been previously discussed, no crossover was allowed between the study arms. GSK does not currently have an up to date consort diagram for this study.

Table 20: Subject Disposition in MEK115306

	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)
Subject status		
Died	40 (19)	55 (26)
Ongoing	154 (73)	147 (69)
On study treatment	111 (53)	90 (42)
In follow-up	43 (20)	57 (27)
Withdrawn from study	17 (8)	10 (5)
Primary reason for withdrawal		
Study closed/terminated	0	0
Lost to follow-up	4 (2)	3 (1)
Investigator discretion	2 (<1)	2 (<1)
Withdrew consent	11 (5)	5 (2)

Fifty-three percent of subjects on the combination treatment arm and 43% of subjects on dabrafenib monotherapy treatment arm were ongoing at the time of data cut-off.

Table 21: Treatment Status for Subjects in MEK115306

	Dabrafenib + Trametinib (N=209)	Dabrafenib + Placebo (N=211)
Trametinib/placebo Treatment		
Treatment status		
Ongoing	111 (53)	90 (43)
Discontinued	98 (47)	121 (57)
Reason for treatment discontinuation		
Disease progression (including death due to disease progression)	74 (35)	102 (48)
Adverse event	17 (8)	10 (5)
Protocol deviation	1 (<1)	0
Study closed/terminated	0	0
Lost to follow-up	0	1 (<1)
Investigator discretion	2 (<1)	1 (<1)
Decision by subject or proxy	4 (2)	7 (3)
Dabrafenib Treatment		
Treatment status		
Ongoing	110 (53)	90 (43)
Discontinued	99 (47)	121 (57)
Reason for treatment discontinuation		
Disease progression (including death due to disease progression)	75 (36)	102 (48)
Adverse event	18 (9)	10 (5)
Protocol deviation	1 (<1)	0
Study closed/terminated	0	0
Lost to follow-up	0	1 (<1)
Investigator discretion	2 (<1)	1 (<1)
Decision by subject or proxy	3 (1)	7 (3)

6.4 Critical appraisal of relevant RCTs

6.4.1 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.

See response to question 6.4.3.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

See response to question 6.4.3. A quality assessment for the comparator RCT used in the Indirect Treatment Comparison (ITC) can be found in Appendix 10.7.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria.

Table 22 presents the critical appraisal of the three RCTs discussed in this submission.

Table 22. Critical appraisal of BREAK-3 (BRF113683), BRF113220 Part C and Combi-d (MEK115306) studies

Critical appraisal criterion	Primary RCT	Supportive RCTs	
	BREAK-3 (BRF113683)[59]	**BRF113220 (Part C)[62]**	**Combi-d (MEK115306)**
Was randomisation carried out appropriately?	Yes. All $BRAF^{V600}$ mutation-positive patients meeting eligibility criteria were randomised 3:1 (open label) to either dabrafenib or dacarbazine. Patients were randomised centrally using the GSK RAMOS IVRS. Method of randomisation and allocation concealment was adequate.	Yes. After subjects were approved to enrol in Part C, they were assigned to study treatment (open-label) in accordance with the randomisation schedule generated by Discovery Biometrics, using the GSK RAMOS (Registration and Medication Ordering System) interactive voice recognition system (IVRS)).	Yes. Upon completion of all the required screening assessments, eligible subjects were registered into the Registration and Medication Ordering System (RAMOS), the GSK interactive voice response system (IVRS), by the investigator or authorized site staff. RAMOS allows study sites to register and randomize subjects, and also records stratification information. Randomization was done centrally using a randomization schedule generated by the GSK Biostatistical Department, which assigned subjects in a 1:1 ratio to either study arm.
Was the concealment of treatment allocation adequate?	Treatment allocation was not concealed as this was an open label study.	Treatment allocation was not concealed as this was an open label study.	Yes. This was a double blind study. A trametinib placebo was used for the study control arm, allowing one arm to be a dabrafenib monotherapy arm while the the study active treatment arm comprised combination therapy with dabrafenib and trametinib.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. Treatment groups were well balanced at baseline in terms of demographic and disease characteristics (e.g. age, gender, histology, organs involved, number of metastatic sites, ECOG performance status, LDH levels).	Yes. Treatment groups were well balanced at baseline in terms of demographic and disease characteristics (gender, ECOG performance status, BRAF mutation status, disease stage, baseline LDH, number of metastatic sites, prior therapy).	Yes. Treatment groups were well balanced at baseline in terms of demographic and disease characteristics (gender, ECOG performance status, BRAF mutation status, disease stage, baseline LDH, number of metastatic sites, prior therapy).
Were the care providers, participants and outcome assessors blind to	BREAK-3 was an open label study, however, the study team was blinded from the efficacy data and any review of	BRF113220 was an open-label study and treatment was not blinded, although a Blinded Independent Central Review	Yes.

treatment allocation?	these data by the study team including statistics and programming was performed on data with scrambled subject numbers to prevent identification of study treatment. Additionally, the independent review of tumour response was blinded to treatment, investigator-assessed response and progression.	(BICR) was introduced following a protocol amendment to support Part C as a potential registration trial. This was used in sensitivity analysis of PFS to address and evaluate potential sources of bias and demonstrate robustness of the effect on PFS.	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. Reasons for withdrawal of patients were reported adequately. Patients mainly withdrew for the following reasons: disease progression; death; adverse events; investigator's discretion; subject decision.	No. Reasons for withdrawal of patients were reported adequately. Patients primarily withdrew from the study due to withdrawal of consent.	No. Reasons for withdrawal of patients were reported adequately. Patients primarily withdrew from the study due to withdrawal of consent.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. The authors reported all the outcomes as specified in the protocol of the study.	No. The authors reported all the outcomes as specified in the protocol of the study.	No. The authors reported all the outcomes as specified in the protocol of the study.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy and safety analyses were performed using appropriate ITT and modified ITT populations, respectively. Since the duration of treatment for a given subject depends on efficacy and tolerability, the duration of follow-up will vary between subjects. All available time-to-event data was analysed using appropriate statistical methods; subjects with shorter treatment and follow-up due to the natural history of their disease or medical necessities of the	Efficacy and safety analyses were performed using appropriate ITT and modified ITT populations, respectively. Missing data was not imputed. Where appropriate, available data was summarised over specified intervals (e.g., from start of treatment until withdrawal from study) using suitable summary statistics.	Efficacy and safety analyses were performed using appropriate ITT and modified ITT populations, respectively. Missing data was not imputed. Where appropriate, available data was summarised over specified intervals (e.g., from start of treatment until withdrawal from study) using suitable summary statistics.

	treatment of their disease were not considered to have missing data. Consequently there was no imputation for missing time-to-event data.		

6.5 Results of the relevant RCTs

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

6.5.1 Overview of clinical evidence

For the purposes of this submission, where possible, Section 6.5 focuses on the latest data cuts available and only endpoints of relevance to the decision problem have been explored, i.e. OS, PFS and ORR.

- The primary evidence underpinning the safety and efficacy of dabrafenib is found within the BREAK 3 study, detailed below.
- Further information from the other RCTs; BRF113220 and the MEK115306 Combi-d study, provide additional data in support of the efficacy and safety of dabrafenib; a narrative is provided below, with more detailed information provided within appendix 10.13.

A summary table of the relevant efficacy endpoints from all RCTs has been provided below in Table 23. Further details in relation to these endpoints have been provided in the relevant sub-sections below for each RCT. Results of OS adjustments for treatment crossover are also provided and are summarised in Table 26.

Table 23. Primary & secondary efficacy endpoints (ITT populations) [BRF113683 (BREAK-3), BRF113220 (Part C) and MEK115306 (Combi-d)]

		Dabrafenib monotherapy (BREAK-3 - BRF113683); NCT01227889 Latest PFS cut-off; 25 Jun 2012[6,76] OS update; 18 Dec 2012[6]		Dual therapy (BRF113220, Part C); NCT01072175 Initial data cut-off: 31 May 2012[7] OS update; 29 March 2013[8]		Combi-d (MEK115306) NCT01584648 Initial data cut off: 26 August 2013	
		Dabrafenib 150mb b.d. (N=187)	**Dacarbazine 1000mg/m^2 (N = 63)**	**Dabrafenib 150mg b.d. *plus* trametinib 2mg o.d. (N=54)**	**Dabrafenib Monotherapy 150mg b.d. (N=54)**	**Dabrafenib 150mg b.d. *plus* trametinib 2mg o.d. (N=211)**	**Dabrafenib 150mg b.d. *plus* trametinib placebo o.d. (N=212)**
Primary outcome(s) & measures	**PFS; months Median (95% CI)**	6.9 (5.2, 9.0)	2.7 (1.5, 3.2)	9.4 (8.6, 16.7)	5.8 (4.6, 7.4)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)
	HR (95% CI); p-value	0.37 (0.24, 0.58); p<0.0001		0.39 (0.25, 0.62)[a,b] ; p<0.001[c]		(0.75; 95%CI: 0.57,0.99); p=0.035	
	ORR (CR + PR); Median (95% CI)	N/A: ORR was not a primary end point in BREAK-3 (see section 6.5.2)		41 (76%) (62.4, 86.5)	29 (54%) (39.6, 67.4)	N/A: ORR was not a primary end point in combi-d (see section 6.5.2)	
	P-value[e]			p=0.0264			
Secondary outcome(s) & measures	**OS; months Median (95% CI)**	18.2 (16.6, NR)	15.6 (12.7, NR)	23.8 (17.5, NR)	20.2 (14.5, 25.9)	NR	NR
	ITT HR (95% CI) P-value	0.76 (0.48, 1.21)[f] p=not significant		0.73 (0.43, 1.24)[d] p=0.2436		N/A	
	Crossover (%)	57		83		N/A	
	RPSFT-adjusted HR (95% CI)	0.55 (0.21, 1.43)		0.47 (0.13, 1.66)		N/A	
	ORR (CR + PR); Median (95% CI)	110 (59) 51.4, 66.0	15 (24) 14.0, 36.2	ORR was not a secondary end point in the BRF113220 study (see section 6.5.2)		140 (67%) (59.9, 73.0)	108 (51%) (44.5, 58.4)
	P-value[e]	No p value given				p = 0.0015	

PFS=progression-free survival, OS=overall survival, ORR=objective response rate, DoR=duration of response, HR=hazard ratio, CR=complete response, PR=partial response, NR=not reached, RPSFT=Rank Preserving Structural Failure Time Model
a. Confidence intervals were estimated using the Brookmeyer Crowley method.
b. Hazard ratio estimated using Pike estimator. A hazard ratio <1 indicates a lower risk with combination compared with monotherapy.
c. P-values are based on 2-sided log rank test. The censoring method included censoring for extended loss to follow-up, new anti-cancer therapy, and excluding symptomatic progression.
d. Based on data cut-off: 29 March 2013; median follow-up time: 24 months
e. P-values and 95% CIs were calculated based on the unconditional exact method.
f. Based on data cut-off: 18 December 2012 median follow-up time (dabrafenib): 15.2 months, (dacarbazine): 12.7 months

6.5.2 BREAK-3 - Efficacy

To summarise, the dabrafenib pivotal trial (BREAK-3) was a randomised two-arm, open-label, phase III study designed to evaluate the safety and efficacy of dabrafenib 150 mg twice daily (n=187) orally compared with dacarbazine 1000 mg/m^2 intravenously every 3 weeks (n=63) in patients with untreated, BRAF V600E mutation-positive, unresectable stage IIIC or stage IV metastatic melanoma. 3:1 randomisation was implemented and crossover was allowed upon progression to mitigate ethical concerns around dacarbazine, a minimally effective treatment in light of emerging clinical data with vemurafenib. The primary outcome in BREAK-3 was investigator-assessed PFS.

At the pre-specified, initial data analysis of 19 December 2011, treatment with dabrafenib resulted in a statistically significant and clinically meaningful improvement in investigator-assessed PFS compared to treatment with dacarbazine, with a hazard ratio of 0.30 (95% CI: 0.18, 0.51; p<0.0001). This represents a 70% reduction in the risk of tumour progression or death for patients treated with dabrafenib compared to dacarbazine.[5] At this point, 21 patients (11%) in the dabrafenib group and 9 (14%) in the dacarbazine group had died. For those subjects who were initially randomised to either dabrafenib or dacarbazine, the number of deaths on treatment increased to 55 patients (29%) and 21 patients (33%), respectively, as of Jun 25, 2012.

At this subsequent 25 June 2012 data cut-off, 35 subjects (55.6%) of the 63 randomised to dacarbazine had crossed over to receive dabrafenib, and 63% of subjects randomised to dabrafenib and 79% of subjects randomised to dacarbazine had progressed or died. The investigator-assessed median PFS had increased from 5.1 months (19 Dec 2011) to 6.9 months in the dabrafenib arm (25 June 2012), while it remained the same at 2.7 months for patients with dacarbazine (HR = 0.37; 95% CI, 0.24–0.58 p<0.0001), see Table 24 and Figure 6. Median PFS after crossover was 4.4 months.

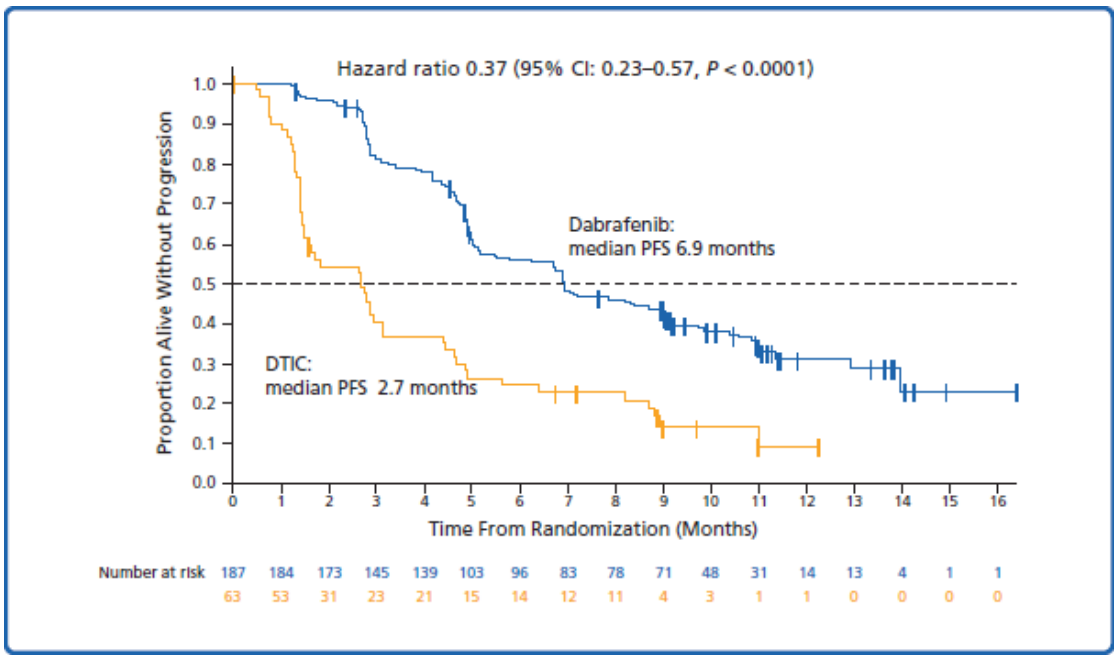
Although response confirmation is not required in RECIST 1.1, the confirmed response rates were also examined in order to compare the results of this study with historical response rates. As of the 25 June 2012 data cut-off, the investigator-assessed ORR was 59% (95% CI: 51.4, 66.0) in the dabrafenib arm compared to 24% (95% CI: 14.0, 36.2) in the dacarbazine arm. Duration of response was 8.0 months (95% CI: 6.6, 11.5) and 7.6 months (95% CI: 5.0, 9.7), respectively.[6]

Table 24. Efficacy data in BREAK-3 (ITT population; 19 December 2011 and 25 June 2012 cut-offs)[6,76]

	Data as of December 19, 2011		Data as of June 25, 2012	
	Dabrafenib N=187	**DTIC N=63**	**Dabrafenib N=187**	**DTIC N=63**
Progression-free survival				
Median, months (95 % CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)	6.9 (5.2,9.0)	2.7 (1.5,3.2)
HR (95 % CI)	0.30 (0.18, 0.51) P < 0.0001		0.37 (0.24, 0.58) P < 0.0001	
Overall response[a]				
% (95 % CI)	53 (45.5, 60.3)	19 (10.2, 30.9)	59 (51.4, 66.0)	24 (14, 36.2)
Duration of response				
Median, months (95 % CI)	N=99 5.6 (4.8, NR)	N=12 NR (5.0, NR)	N=110 8.0 (6.6, 11.5)	N=15 7.6 (5.0, 9.7)

Abbreviations: CI: confidence interval; DTIC: dacarbazine; HR: hazard ratio; NR: not reached

a. Defined as confirmed complete +partial response.



- On randomized study treatment at cut-off: dabrafenib 38%, DTIC 8%
- Median follow-up time: dabrafenib 10.5 months, and DTIC 9.9 months
- Median PFS following crossover was 4.4 months (n = 35; 95% CI: 4.1–6.3)

Figure 6. PFS investigator-assessed in BREAK-3 (ITT population; 25 June 2012 cut-off)[6]

The PFS benefit associated with treatment with dabrafenib was observed consistently across all pre-specified subgroups analysed (19 December 2011 data cut-off), including those with $M1_c$ disease; typically associated with particularly poor prognosis (Figure 7).[59]

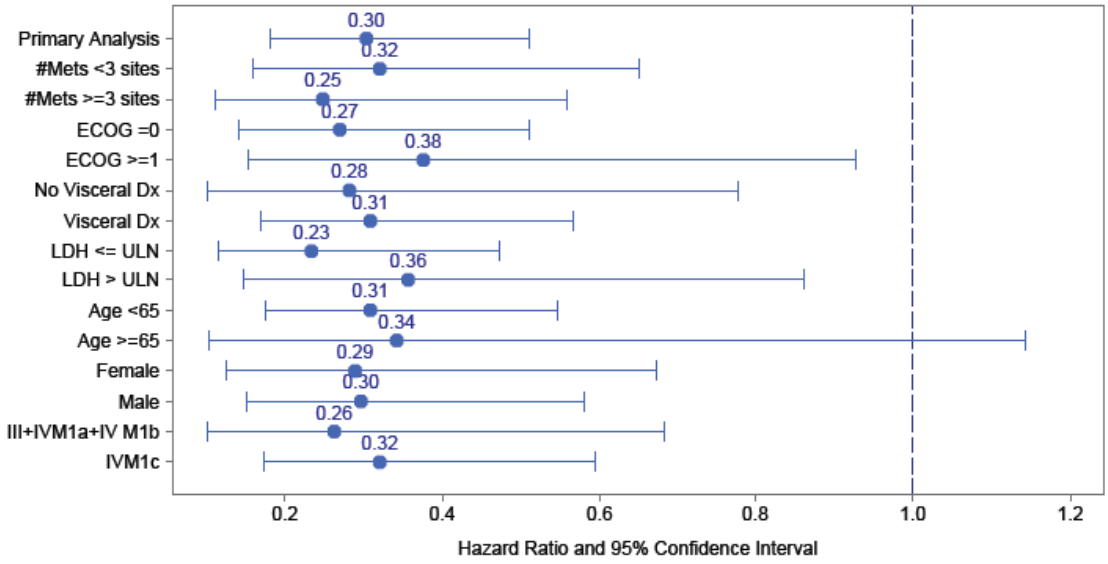


Figure 7. Investigator-assessed PFS sub-analysis in BREAK-3 (ITT population; 19 December 2011 cut-off)[59]

As of the June 25, 2012 data cut-off (median follow-up: 10.5 months for dabrafenib, 9.9 months for dacarbazine) a total of 35 out of 63 patients (56%) had crossed over on disease progression from dacarbazine to dabrafenib. The number of patients who had died on treatment with dabrafenib and dacarbazine increased to 55 patients (29%) and 21 patients (33%), respectively.[6]

Despite 56% of patients crossing over from dacarbazine to dabrafenib upon disease progression, an unadjusted OS analysis of data collected up to Jun 25, 2012 demonstrated an improvement in OS with dabrafenib compared to dacarbazine with a HR of 0.75 (95% CI: 0.44–1.29). This represents a 25% reduction in the risk of death for patients treated with dabrafenib compared with those treated with dacarbazine.[6]

The Kaplan-Meier estimates of OS at 6 and 9 months were 86% (95% CI: 79.8, 91.0) and 78% (95% CI: 71.2, 83.4) in the dabrafenib arm, respectively whereas the estimates were 85% (95% CI: 72.3, 91.6) and 74% (95% CI: 60.4, 83.4) in the dacarbazine arm.

The OS estimates for dacarbazine includes patients who crossed over to dabrafenib and thus reflecting a benefit of second-line dabrafenib. Due to the crossover patients in BREAK-3, comparisons of OS are confounded by the subsequent treatment of crossover patients with dabrafenib, as previously discussed.

At the latest clinical data cut-off (18 December 2012; median follow-up: 15.2 months for dabrafenib, 12.7 months for dacarbazine), 12-month OS rates were 70% for dabrafenib versus 63% for dacarbazine.[6] (Figure 8); 55.6% of the dacarbazine subjects had crossed over to dabrafenib). Median OS was 18.2 months (95% CI; 16.6, NR) and 15.6 months (95% CI; 12.7, NR) for dabrafenib and dacarbazine, respectively (HR 0.76 (95% CI; 0.48, 1.21) (Figure 8).

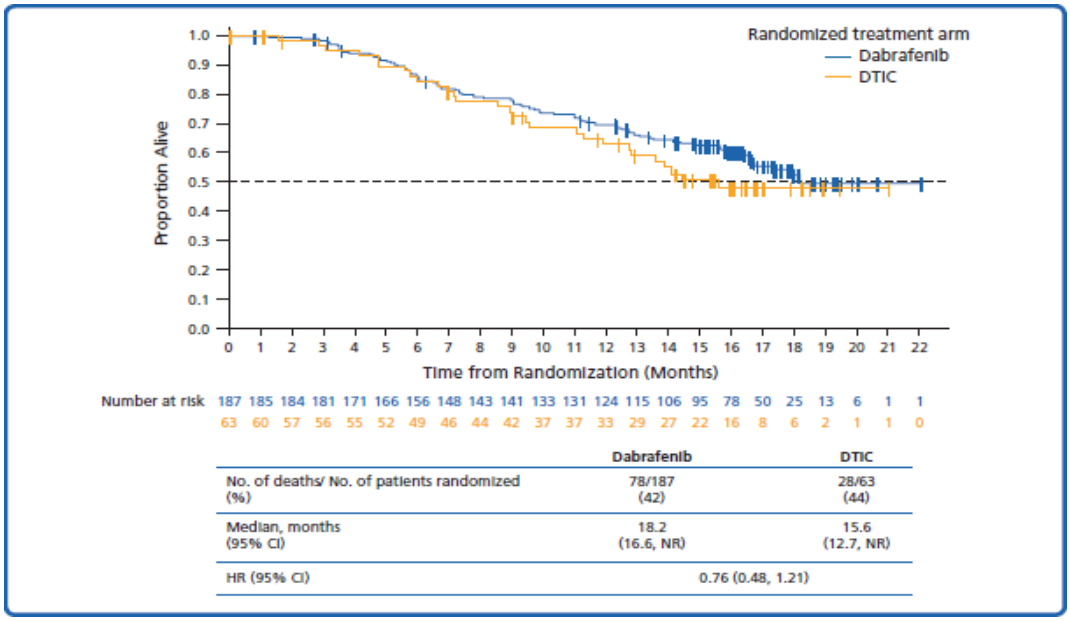


Figure 8. Unadjusted OS for BREAK-3 (ITT population, 18 December 2012 cut-off) [6]

To account for the confounding effect of crossover on OS in BREAK-3, the RPSFT analysis revealed an adjusted OS HR of 0.55 (95% CI; 0.21, 1.43), demonstrating a clinically relevant reduction in the risk of death versus dacarbazine. This is subsequently utilised in the economic model (Section 7). A comparative table of adjusted results for OS from all RCTs have been provided in Table 26.

Health-related quality of life (HRQoL) was assessed in BREAK-3 using the EQ-5D utility index. EQ-5D data were collected at screening, Week 6, Week 12, Week 15, at disease progression, and at approximately 30 days after progression; (See Section 6.3.5 for methodologies). A summary of these data is presented in Table 25.[48,77]

Table 25. Descriptive statistics on EQ-5D utility index in the BREAK-3 study

Treatment	N	Time	N	Mean	SD	Median	Min.	Max.
Dabrafenib	187	Baseline	184	0.724	0.266	0.752	-0.32	1.00
		Week 6	165	0.774	0.215	0.796	-0.08	1.00
		Week 12	136	0.795	0.193	0.796	-0.07	1.00
		Week 15	135	0.777	0.206	0.796	0.00	1.00
		Progression	37	0.599	0.355	0.689	-0.22	1.00
		Week 4 Post-PD	8	0.839	0.256	0.942	0.26	1.00
Dacarbazine	63	Baseline	59	0.717	0.309	0.760	-0.24	1.00
		Week 6	33	0.787	0.248	0.848	-0.07	1.00
		Week 12	19	0.824	0.179	0.848	0.49	1.00
		Week 15	18	0.845	0.163	0.848	0.52	1.00
		Progression	26	0.671	0.299	0.725	-0.07	1.00
		Week 4 Post-PD	3	0.701	0.394	0.848	0.26	1.00

Post-PD=post-progressive disease, SD=standard deviation

Supportive RCTs – Efficacy

Efficacy data for BRF113220 and MEK115306 (Combi-d) are provided in appendix 10.13. Relevant data for the dabrafenib arms of these studies are discussed in the narrative below.

The BRF113220 study

At the time of the pre-specified efficacy analysis (May 31, 2012), median follow-up for patients in Part C of BRF113220 was 14.1 months (range 10.8 - 17.6 months). Treatment with dual therapy 150/2 resulted in a statistically significant and clinically meaningful improvement in investigator-assessed PFS of 3.6 months compared to treatment with dabrafenib monotherapy, the primary efficacy endpoint. The median PFS in the 150/2 group was 9.4 months (95% CI; 8.6, 16.7) and in the dabrafenib monotherapy groups was 5.8 months (95% CI; 4.6, 7.4) (Table 23).

Analysis of the overall response rates demonstrated a statistically significantly higher investigator-assessed ORR in the dual therapy 150/2 group, as compared with the monotherapy group (76% vs. 54%; p=0.03). The findings for dabrafenib monotherapy in the BRF113220 study broadly support the response rate observed in the BREAK-3 study (59%; June 2012 data cut-off).

Median overall survival (OS) had not been reached at the time of the initial analysis (31 May 2012; median follow-up time of 14 months; 51 deaths). The percentage of patients who were alive at 12 months was 79% in the dual therapy 150/2 group and 70% in the monotherapy group, even though 80% of patients in the monotherapy group crossed over to the dual therapy 150/2 group at the time of disease progression.

At the time of a post-hoc analysis from a 29 March 2013 data cut-off (median follow-up; 24 months), 51% of patients had died (83/162) across all three arms and 18 (33%) patients in the 150/2 dual therapy arm were ongoing on study treatment. It should be noted that, by this time, 83% of the dabrafenib monotherapy (150 mg b.d.) population had crossed over to receive dual therapy (150/2) following disease progression. A comparison of survival rates between the 150/2 and the dabrafenib monotherapy arms of the study yields a HR of 0.73 (95% CI; 0.43, 1.24; p=0.24).

The true magnitude of effect of dual therapy on OS is likely to have been substantially confounded by the high degree of crossover (83%) at the time of this analysis. When RPSFT analysis was applied to adjust for this confounding effect, analysis revealed a crossover-adjusted OS HR of 0.47, (95% CI 0.13, 1.66).

HRQoL data were not collected during this study since this is a Phase II study and was not initially designed as a registration trial.

MEK115306 (Combi-d) study

At the time of the pre-specified primary efficacy analysis (26 August 2013), median follow-up for patients in both arms of the study was around 9 months.The primary analysis of efficacy endpoints (PFS) was based on the primary efficacy population in the Combi-d study, which was a sub-population of the overall ITT population. This included patients with $BRAF^{V600E}$ and $BRAF^{V600K}$ mutation. At the time of writing, a summary of the data from the primary analysis has been placed in the public domain. A comprehensive Clinical Study report had not been produced for this study at the time of this submission. For consistency with the requirements of section 6.5, the efficacy results and Kaplan Meier curves from the ITT population are presented in Table 6 and Figure 6 of Appendix 13, respectively.

PFS analysis by investigator assessment was based on events in approximately one-half of subjects in each treatment arm (dual therapy: 102 events, 48%; monotherapy: 109 events, 51%).

Median PFS for the combination arm was 9.3 months compared to 8.8 months for the monotherapy arm. The HR for PFS (0.75; 95%CI: 0.57, 0.99) in the Combi-d study was statistically significant (p=0.035) (Table 6; Figure 6). As of January 15, 2014, there are 245 (58%) PFS events observed across two treatment arms.

The BIRC assessment was a protocol-specified sensitivity analysis. The PFS results from the BIRC assessment were generally consistent with that observed by investigator-assessment (Table 6; Figure 7). The BIRC assessment was based on events in 44% of subjects in each treatment arm. The median PFS was 10.1 months for the combination arm and 9.5 months for the monotherapy arm.

Pre-planned sensitivity analyses demonstrated consistency with the hazard ratio (0.71-0.73) and median estimates on the combination arm (9.2-9.3) reported in the primary analysis. However, the number of subjects with symptomatic progression or new anticancer therapy prior to documented radiological progression was higher on the dabrafenib monotherapy arm resulting in median estimates which were lower (7.2-7.6) as compared to the primary analysis. A more detailed explanation is provided in Appendix 13.

The ORR results as determined by the investigators showed a 15% absolute difference in the combination arm compared to the monotherapy arm. This difference was statistically significant (p=0.0015). The ORR results for the monotherapy arm are similar to those in other dabrafenib monotherapy trials. The ORR results for MEK115306 as assessed by the BIRC were similar to the investigator assessed results and also statistically significant.

Finally, the planned interim analysis of overall survival was conducted with 40 deaths (19%) in the combination arm and 55 deaths (26%) in the monotherapy arm (Table 9; Figure 8). In this analysis, an effect favouring the combination arm was observed with a HR of 0.63 (95% CI, 0.42, 0.94). With a median follow-up time of approximately 9-months on each arm, the median OS point estimates have not yet been reached.

The final OS analysis will be performed when 70% of the subjects have died or been lost to follow up, which is expected to consist of 275 deaths; aassuming a 5% lost to follow-up rate. As of 15 January 2014, 137 deaths (32%) had been reported.

Efficacy Conclusions

In BREAK-3, treatment with dabrafenib was shown to be superior over dacarbazine in all of the efficacy endpoints in patients with unresectable stage IIIC or IV metastatic $BRAF^{V600E}$ mutation positive melanomas. Specifically, the hazard ratio comparing investigator-assessed PFS between dabrafenib and dacarbazine was 0.37 (95% CI: 0.24, 0.58) at the latest data cut-off;June 2012. This represents a 63% reduction in the relative risk of tumour progression or death with dabrafenib compared to dacarbazine. The PFS benefit associated with treatment with dabrafenib was observed in patients with M1c disease, which is associated with particularly poor prognosis. The investigator-assessed median PFS was 5.1 months in the dabrafenib arm at the December 2011 cut-off and increased to 6.9 months in June 2012, while it remained the same at 2.7 months in the dacarbazine arm. This demonstrates a PFS benefit associated with dabrafenib treatment that is consistent with the magnitude of benefit derived with vemurafenib during the BRIM-3 study.[31,37,38] All pre-specified subgroup analyses and covariates showed a consistent PFS benefit of the same magnitude as the overall study population for dabrafenib in each subgroup.

The analysis of overall response rates (complete and partial response rates) further supported the PFS data as there was a difference in ORR of 35% in favour of dabrafenib compared to dacarbazine (95% CI: 20.9, 48.7).

Although, due to high levels of crossover in the study, there are no statistically significant differences in OS, the analysis numerically favours dabrafenib over dacarbazine. It is also widely accepted that there is a strong correlation between OS and PFS which was recently demonstrated in metastatic melanoma by Flaherty et al[78]. They conducted statistical and meta- analysis on 12 publications of controlled randomized trials which established PFS as a surrogate for overall survival.[78] It is important to note that OS was a secondary endpoint therefore the BREAK-3 trial was not designed or powered to detect a statistically significant difference for OS. Nonetheless all three analyses at the date cuts of December 2011, June and December 2012 consistently showed a positive trend towards in OS in favour of dabrafenib. This was despite 57% of dacarbazine subjects crossing over to the dabrafenib treatment at the time of radiographic progression.

The updated analysis from Dec 2012 showed a median OS of 18.2 months for dabrafenib and 15.6 for dacarbazine and a hazard ratio of 0.76 (95% CI: 0.48, 1.21). When an adjustment for crossover was applied, this HR decreased to 0.55 (95% CI: 0.48, 1.21).

With regards to the supporting RCTs, the first data cut-off (31 May 2012) for BRF113220 demonstrated a median PFS for dabrafenib of 5.8 months, which was not dissimilar to the two PFS values reported from the BREAK-3 study; 5.1 months (95% CI:4.9, 6.9) (Dec 2011) and 6.9 months (95% CI 5.2, 9.0) (June 2012). The variation is likely due to differences in the median length of follow-up (Table 10). This similarity across studies demonstrates some consistency in the benefit to patients receiving dabrafenib. This magnitude of benefit is comparable to the findings for vemurafenib from the BRIM-3 study; 6.9 months (95% CI 6·1, 7·0) of PFS (see section 6.7).[79] The HR from the BREAK-3 study for PFS was 0.37 (95% CI: 0.24, 0.58); p<0.0001 is also comparable to the HR from the BRIM-3 study, 0·38 (95% CI: 0·32–0·46); p<0·0001).

The overall response rates shown by dabrafenib also show remarkable consistency. While the BREAK-3 study showed an ORR of 59%, the dabrafenib arms of the

BRF113220 study and the Combi-d study showed 54% and 51% respectively. This again shows some concordance with the latest data from BRIM 3 where the comparable ORR was 57%.[79]

Finally, while the data is still too immature to show overall survival in the Combi-d study, the BRF113220 study showed overall survival of 20.2 months (95% CI; 14.5, 25.9) in patients who received dabrafenib monotherapy. The value is highly likely to be confounded as 83% of patients being treated with dabrafenib crossing over to receive the combination treatment of dabrafenib (150mg) and trametinib (2mg). With the BREAK 3 study showing overall survival of 18.2 months (95% CI; 16.6, NR), it is plausible that the true estimate of overall survival would lie somewhere within this range of values.

6.5.3 OS results adjusted for confounding effects of crossover on overall survival

Results for all adjustments for crossover of all data cut-offs from BREAK-3 and BRF113220 and are shown in Table 26.

Table 26. Results (HR, 95% CI) of comprehensive crossover adjustments for BREAK-3 and BRF113220 OS data (input to ITC shaded in grey)

Method type	Description	BREAK-3 trial (dabrafenib monotherapy)		BRF113220 study (dual therapy)	
		June 2012	Dec 2012	May 2012	Mar 2013
1. ITT	Intention to treat analysis (to provide a 'baseline' analysis)	0.75, 0.45 – 1.24	0.76, 0.49 – 1.18	0.67, 0.34 – 1.34	0.73, 0.43 -1.24
2. Naive	Censor crossover patients at time of crossover	1.20, 0.54 – 2.65	1.37, 0.66 – 2.85	1.33, 0.43 – 4.15	1.41, 0.52 -3.79
3. Naive	Exclude crossover patients	0.93, 0.42 – 2.05	1.07, 0.52 – 2.22	0.58, 0.19 – 1.76	0.60, 0.23 - 1.59
4. Naive	Include experimental treatment received as a time-dependent covariate	1.26, 0.58 – 2.76	1.49, 0.72 – 3.08	1.88, 0.65 – 5.49	1.90, 0.74 - 4.88
5. Naive	Include treatment crossover indicator as a time-dependent covariate	1.15, 0.52 – 2.54	1.35, 0.65 – 2.80	1.42, 0.46 – 4.40	1.54, 0.58 - 4.10
6. Complex	RPSFT 'treatment group' analysis. This estimates an average treatment effect of being allocated to the experimental group, adjusted for crossover.	0.52, 0.17 – 1.61	0.55, 0.21 – 1.43	0.49, 0.14 – 1.69	0.47, 0.13 - 1.66
7. Complex	RPSFT 'on treatment' analysis. This estimates the average treatment effect of full treatment (no discontinuation) compared to no treatment.	0.34, 0.05 – 2.19	0.27, 0.03 – 2.19	0.65, 0.31 – 1.37	0.36, 0.06 - 2.00
8. Complex	RPSFT 'on treatment - observed' analysis. This estimates the average treatment effect of observed experimental treatment compared to no treatment, assuming an effect is only received while on treatment.	0.57, 0.22 – 1.50	0.55, 0.21 – 1.43	0.72, 0.19 – 1.57	0.49, 0.15 - 1.63
9. Complex	IPE Algorithm 'treatment group' analysis. This estimates an average treatment effect of being allocated to the experimental group, adjusted for crossover.	0.52, 0.18 – 1.55	0.50, 0.15 – 1.64	0.50, 0.15 – 1.62	0.50, 0.16 - 1.54
10. Complex	IPE Algorithm 'on treatment' analysis. This estimates the average treatment effect of full treatment (no discontinuation) compared to no treatment.	0.36, 0.06 – 1.99	0.22, 0.02 – 2.90	0.65, 0.02 – 2.84	0.34, 0.06 - 1.99
11. Complex	IPE Algorithm 'on treatment - observed' analysis. This estimates the average treatment effect of observed experimental treatment compared to no treatment, assuming an effect is only received while on treatment.	0.60, 0.26 – 1.41	0.50, 0.15 – 1.63	0.72, 0.16 – 1.61	0.47, 0.14 - 1.61

6.6 Meta-analysis

6.6.1 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).

A meta-analysis was not conducted as there was only one randomised controlled trial for the intervention verus a relevant comparator, BREAK-3.

6.6.2 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.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (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.

Not applicable.

6.7 Indirect and mixed treatment comparisons

6.7.1 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 10.4, appendix 4.

Details of the search strategies and methodology employed to identify relevant clinical data on comparators can be found in Section 6.1. A broad literature review was undertaken (initially searched in October 2012, updated in October 2013) to evaluate the relative efficacy and safety of dabrafenib and trametinib (monotherapies and in combination) compared to ipilimumab, dacarbazine, vemurafenib, and fotemustine for the treatment of metastatic melanoma. For the purposes of this decision problem, only the comparisons of dabrafenib (as a monotherapy) with vemurafenib and dacarbazine are considered relevant (see Section 5). Published literature from the update search was screened only for any new evidence relating to relevant interventions or comparators, and quantitative analyses (ITCs and crossover adjustments) were updated to include the most recent available data.

Indirect treatment comparisons were undertaken for dabrafenib versus vemurafenib.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Two trials were included in the indirect treatment comparison. BREAK-3 (dabrafenib pivotal trial) is described in sections 6.3 – 6.5. The comparator trial – BRIM-3 – is described below in detail in Table 27 - Table 30.

The BRIM-3 study was an open-label, parallel-group, active-comparator RCT assessing the efficacy of vemurafenib (Roche's BRAF inhibitor) versus dacarbazine in which 675 patients were randomly assigned in a 1:1 ratio. At the time of the interim analysis (December 2010), the data and safety monitoring board recommended that patients in the dacarbazine group be allowed to cross over to receive vemurafenib (leading to a protocol amendment on January 14th, 2011). BRIM-3 is described in detail in the tables below.

The BRIM-3 trial was a robust, phase III randomised controlled trial. See details of the critical appraisal of this study in Appendix **Error! Reference source not found.**.

Table 27. BRIM-3 study details

	Year	Study design	Intervention	Comparator	Population	Patient crossover
Vemurafenib (BRIM-3 trial)[37]	2011	Multi-centre, open-label (although allocation concealed), phase III RCT	Vemurafenib 960 mg bid (n=337)	Dacarbazine 1000 mg/m2 (n=338)	Treatment-naive adults with metastatic melanoma (surgically incurable and unresectable Stage IIIC or Stage IV) with $BRAF^{V600}$ mutation-positive disease	Patient crossover (dacarbazine to vemurafenib) at each data cut: Dec 2010: 0% Mar 2011: 15% Oct 2011: 24% Feb 2012: 34%

Table 28. Eligibility criteria for BRIM-3

	Inclusion criteria	Exclusion criteria
Vemurafenib (BRIM-3 trial)[37]	• Treatment-naive patients ≥ 18 years of age with histologically confirmed unresectable stage IIIC or stage IV melanoma • Must have had a $BRAF^{V600}$ positive mutation (by Roche Cobas test) • ECOG performance status of 0 or 1 and life expectancy > 3 months • adequate haematologic, hepatic, and renal function	• History of cancer within the past 5 years (except for basal- or squamous-cell carcinoma of the skin or carcinoma of the cervix) or metastases to the central nervous system, unless such metastases had been definitively treated more than 3 months previously with no progression and no requirement for continued glucocorticoid therapy. • Concomitant treatment with any other anticancer therapy was not allowed.

Table 29. Characteristics of BRIM-3 participants

	Vemurafenib (N = 337)	Dacarbazine (N = 338)
Median age (yr)	56 (21–86)	52 (17–86)
Male sex n (%)	200 (59)	181 (54)
White race n %	333 (99)	338 (100)
Geographic region n (%)		
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 n (%)		
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)

ECOG = Eastern Cooperative Oncology Group

Table 30. Endpoints and results of BRIM-3 study

Study outcomes and analysis	Results
• Primary outcomes: OS and PFS ○ OS comparison of treatment groups using unstratified log-rank test (two-sided) ○ HRs estimated using Cox regression ○ Median OS and PFS estimated using KM • Secondary outcomes: ○ best overall response rate (BORR) – defined as a complete response or partial response (confirmed with RECIST); difference between groups in this endpoint assessed using Chi-squared test with Schouten correction ○ duration of response (time from date of earliest response to progression or death); formal hypothesis testing not performed (log-rank for description only) ○ time to response (time from randomisation to earliest qualifying response); no formal hypothesis testing ○ tolerability and safety, PK profile and validation of $BRAF^{V600}$ mutation test, HRQoL, evaluation of biomarkers	*Overall survival* • Median OS (months, Oct 2011): 13.2 v 9.6 • OS HR (Dec 2010): 0.37, 0.26 to 0.55 • OS HR (Mar 2011): 0.44, 0.33 to 0.59 [censoring 50 patients who crossed over from dacarbazine to vemurafenib] *Progression-free survival* • Median PFS (months, Dec 2010): 5.3 vs. 1.6 • HR (Dec 2010): 0.26, 0.20 to 0.33

6.7.3 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.

The relative treatment effects of dabrafenib versus andvemurafenib and dabrafenib were explored through three separate indirect treatment comparisons utilising the four currently available interventional studies for these treatments (BRF113220, BRIM-3, BREAK-3 and METRIC). Table 31 and Figure 9 below summarise this.

Table 31. Summary of the trials used to conduct the indirect comparison

No. trials	Trials	vemurafenib	dabrafenib	Dacarbazine
1	BRIM-3[37]	✓	X	✓
1	BREAK-3[5]	X	✓	✓

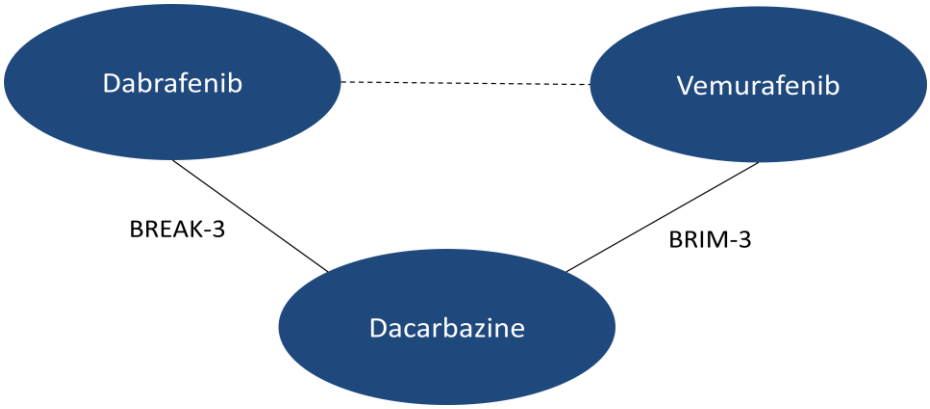


Figure 9. Evidence network and indirect treatment comparisons

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

PFS

The ITCs of PFS included the most up-to-date data on this outcome from the relevant studies, as reported in

Table 32. Heterogeneity is discussed in Section 6.7.7.

Table 32. PFS inputs for indirect treatment comparisons

Study	Datacut	Treatment	Control	HR	95% CI		P
					Lower	Upper	
BREAK-3[5]	Jun 2012	Dabrafenib	Dacarbazine	0.37	0.23	0.58	<.0001
BRIM-3[37]	Feb 2012	Vemurafenib	Dacarbazine	0.38	0.32	0.46	<.001

OS

Inputs for the ITCs of OS data were the most recent (where possible) crossover-adjusted results from the relevant studies, not the results of intention-to-treat analyses. As described in Section 6.3.6, BREAK-3 allowed patients randomised to the control arm to receive the investigational treatment upon initial progression. The same applies to the BRIM-3 trial of vemurafenib (see Table 33 below).

Table 33. Level of patient crossover at different data points for BRIM-3

	BRIM-3			
Datacut (date)	Dec 2010	Mar 2011	Oct 2011	Feb 2012
% control group crossing over on progression (%)	0	15	24	34
Median OS (months) ***in control arm*** (ITT, unadjusted result)	7.8	7.9[¥]	9.6[¥]	10.3*

* Roche response to ACD 1 – July 2012

[¥] Slides presented at vemurafenib STA ACM 2 – July 2012

The RPSFT-adjusted HR for OS from the most recent datacut of the BRIM-3 trial (February 2012) was reported in the manufacturer's response to their first ACD.[**] This result (HR 0.64, 95% CI 0.53 to 0.78) and the other ITC inputs for OS are summarised in Table 34 below. There is no universally accepted way to adjust for crossover and the comprehensive approach taken in this submission is described in Section 6.3.6. In summary, the RPSFT method was deemed most appropriate for these datasets.

Table 34. OS inputs for indirect treatment comparisons

	Reference	Treatment	Control	HR*	95% CI	
					Lower	Upper
BREAK-3	Section 6.3.7	dabrafenib	Dacarbazine	0.55	0.21	1.43
BRIM-3*	Section 6.3.7	vemurafenib	Dacarbazine	0.64	0.53	0.78

[**] Roche response to first ACD (7th July 2012): http://www.nice.org.uk/nicemedia/live/13579/60480/60480.pdf

GSK have identified a potential inconsistency in the estimate of the crossover-adjusted 95% CI for BRIM-3. Assuming that the lognormal HR (ln(HR)) for OS is distributed normally, the 95% CI on the HR for the RPSFT analysis of OS reported by the manufacturer (0.53-0.78) implies a standard error (SE) on the ln(HR) of 0.117 which is virtually identical to that implied by the 95% CI on the HR for the ITT analysis of OS (0.118). Any differences between these two values are likely a consequence of rounding. As the RPSFT method maintains the p-value of the unadjusted (ITT) analysis, if the measure of treatment effect increases with the RPSFT analysis (as it does for the RPFST analysis of OS from BRIM-3, from a 24% reduction to a 36% reduction in hazards of death), then the SE on the treatment effect must, by definition, increase. Accordingly, the 95% confidence half width on the RPSFT HR is likely underestimated. The methods by which the manufacturer obtained the 95% CI and p-value for the RPSFT analysis of OS were not reported.

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

Indirect comparisons of PFS and OS were undertaken using the adjusted indirect comparison methodology described by Bucher.[80]

This method can provide an unbiased comparison of two treatments by combining the direct comparisons of each treatment with respect to their common control group, or combining direct and indirect evidence in a step-wise way.

The mathematical equation for the indirect treatment comparison is:

HR of treatment A vs. treatment C: $HR_{AC}=HR_{AB}/HR_{CB}$

95% CI estimated under the assumption:

$$Var(\ln HR_{AC}) = Var(\ln HR_{AB}) + Var(\ln HR_{CB})$$

The underlying similarity assumption of the Bucher method requires that study or patient characteristics which are treatment modifiers are similar between the trials being compared. The BREAK-3 and BRIM-3 trials were similar in many respects, although differed in median follow-up time at their latest datacuts (see Table 35). We deemed them comparable enough to meet the assumptions required for the Bucher ITC.

Table 35. Datacuts utilised in indirect treatment comparisons

	BREAK-3[6,59](dabrafenib)	BRIM-3[40]
PFS data cut	June 2012	Feb 2012
Median follow-up – experimental arm (months)	10.5	12.5
Median follow-up – control arm (months)	9.9	9.5
OS data cut	Dec 2012	Feb 2012
Median follow-up – experimental arm (months)	15.2	As above

Median follow-up – control arm (months)	12.7	As above

6.7.6 Please present the results of the analysis.

The results of the ITCs of dabrafenib versus vemurafenib are shown below in Table 36.

Table 36: Adjusted ITC of the HR for PFS for dabrafenib vs. vemurafenib

	Treatment	Control	HR	95% CI	
				Lower	Upper
ITC	Dabrafenib	Vemurafenib	0.97	0.59	1.60

*Values are rounded for illustration. Actual ("unrounded") values are used in the model.

The results of the indirect treatment comparisons of OS for dabrafenib and trametinib as monotherapies versus vemurafenib using the most mature crossover adjusted OS data available are shown below in Table 37.

Table 37: ITCs of RPSFT-adjusted OS for dabrafenib vs. vemurafenib

	Treatment	Control	HR	95% CI	
				Lower	Upper
ITC	Dabrafenib	Vemurafenib	0.86	0.32	2.29

*Values are rounded for illustration. Actual ("unrounded") values are used in the model.

The results of the ITCs of OS have wide confidence intervals, in part because of the immaturity of the underlying OS data from and because the RPSFT adjustment maintains the p-value of the ITT analysis.

The results from the ITCs provide no clear evidence of any difference in efficacy between the two BRAF inhibitors. In the base case we utilise the point estimates from the ITCs. The scenario analysis in which a class effect is assumed between the two BRAF inhibitors is incorporated in the deterministic sensitivity analyses.

The PFS results (medians and HRs) for vemurafenib and dabrafenib are almost identical and a comparison of the smoothed hazards and time-dependent HRs for OS over the common follow-up for OS of the two trials (as shown in Figure 10) suggest the patterns of the hazards and HRs are similar. This conclusion of similar treatment effects for dabrafenib and vemurafenib is further supported by a comparison of response data between BREAK-3 and BRIM-3. In BREAK-3, 59% of dabrafenib and 24% of dacarbazine patients had a complete or PR (at June 2012 datacut) while in BRIM-3 (February 2012 datacut), 48% of vemurafenib and 5% of dacarbazine patients had a confirmed response. Taken as a whole, these data provide no strong evidence to suggest that dabrafenib is not at least as effective as vemurafenib. In the face of this uncertainty, the base case utilises the results of the ITC of dabrafenib versus vemurafenib and we provide a scenario analysis utilising a class effect assumption.

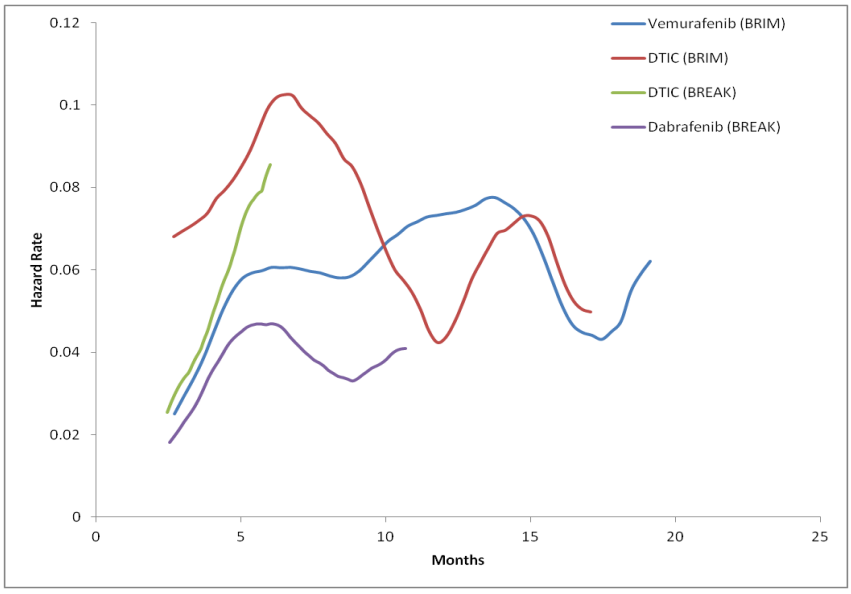


Figure 10. Kernel smoothed hazard rates for RPSFT adjusted OS from BRIM-3 and BREAK-3

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

Inputs into the ITCs were not based on pooled efficacy results/meta-analyses from multiple studies of interventions so there are no formal assessments of heterogeneity associated with these quantitative analyses.

However, in the absence of statistical assessments of heterogeneity, we identify factors that could lead to heterogeneity between the studies being compared:

- Sample sizes (BREAK-3: n=250; BRIM-3: n=675)
- Ratio of randomisation (BREAK-3 3:1; BRIM-3 1:1)
- Different time-points (cut-off dates) of assessment (see Table 35).

It is unclear what implication these factors would have on the results observed above.

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

Not applicable.

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

Not applicable

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 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 10.6 and 10.7, appendices 6 and 7.

See Section 6.2.7 for a list of the non-RCTs considered in relation to this appraisal. Below is a summary of the approach taken with regards to the selection of the non-RCTs which are considered appropriate to this appraisal. A more detailed summary is provded in appendix 10.14.

BREAK-2 (NCT01153763; BRF113710) was an open-label, single-arm study evaluating the efficacy and safety of dabrafenib monotherapy, which provided additional supportive evidence of activity in patients with $BRAF^{V600}$ mutation-positive metastatic melanoma.[57] This provided further justification for the Phase III study to investigate the efficacy and safety of dabrafenib versus standard dacarbazine chemotherapy in this population (i.e. the BREAK-3 study).

BREAK-MB (BRF113929; NCT01266967) evaluated the safety and efficacy of dabrafenib in patients with stable brain metastases.[4] Whilst the population with brain metastases is significant at around 20%, with almost 50% developing these during the course of their disease, in themselves they do not constitute a specific sub-population for either the licensed indication for dabrafenib or for the scope of this NICE appraisal. The staging of brain metastases classifies brain metastases as AJCC (American Joint Committee on Cancer) M1c[19], together with other non-lung visceral metastases. It should be noted that the licensed indication for dabrafenib does not separate out a sub-population of patients with brain metastases. Therefore this study was not deemed relevant to the decision problem, but may be clinically relevant to oncologists and patients.

BREAK-2 study[57] – efficacy findings

The main purpose of the single-arm study BRF113710 (BREAK-2) was to evaluate the efficacy and safety of dabrafenib (gelatin capsules) in subjects with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation positive metastatic melanoma. The primary objective of the study was to assess the ORR, defined as the proportion of subjects with investigator-assessed complete response (CR) or partial response (PR), in subjects with $BRAF^{V600E}$ mutation positive metastatic melanoma treated with dabrafenib.

Subjects were treatment-naïve or received prior treatment in the metastatic setting (i.e., chemotherapy, immunotherapy, prior targeted therapy, etc.). The primary analysis was based on the confirmed investigator-assessed ORR in subjects with V600E mutation positive metastatic melanoma.

Subjects received dabrafenib 150 mg BID and continued on treatment until disease progression, death, or unacceptable adverse event (AE).

A total of 211 subjects were screened for enrollment; 92 subjects with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation-positive melanoma entered into the study; Seventy-six subjects with V600E mutation positive metastatic melanoma and 16 subjects with V600K mutation positive metastatic melanoma were enrolled.

A total of 45 subjects (59%) in the BRAF V600E Population had a confirmed response (95% CI: 48.2-70.3%). Stable disease was defined as having a minimum of 12 weeks of SD.

Per the independent radiologist assessment, the median PFS in the $BRAF^{V600E}$ Population was 26.7 weeks. The median PFS as assessed by both the investigator and the independent radiologist is similar. With 38% of the subjects ongoing and a large number of subjects censored around the median PFS, the maturity of the data had not yet been established at the time of the analysis. The median PFS in the $BRAF^{V600K}$ Population based on independent review is 19.7 weeks.

As a secondary endpoint, the median PFS in the BRAF V600E population was 27.4 weeks. With 39% of the subjects ongoing and a large number of subjects censored around the median PFS, the data was not mature at the time of the analysis. The median PFS in the $BRAF^{V600K}$ Population was 19.7 weeks.

With a median follow-up time of 6.5 months, 70% of the $BRAF^{V600E}$ Population and 62% of the $BRAF^{V600K}$ Population was alive at the time of the data cut-off. The OS data was not mature at the time of the analysis and the median OS estimate could be accurately determined.

BREAK-MB study[4] – efficacy findings

The BREAK-MB study was a global, multi-center, open-label, two-cohort, Phase II study designed to prospectively evaluate the activity of dabrafenib in subjects with histologically confirmed (Stage IV) BRAF-mutation positive (V600E or V600K) melanoma metastatic to the brain.

The primary objective of the study was to assess the overall intracranial response rate (OIRR), defined as the proportion of subjects with confirmed complete or partial intracranial responses assessed by investigators in each of two cohorts of subjects

with BRAFV^{600E} or BRAF^{V600K} mutation-positive metastatic melanoma to the brain treated with oral dabrafenib, using the modified RECIST 1.1 criteria for each cohort.

A total of 172 subjects with V600 mutation-positive melanoma (V600E mutation: 139 subjects; V600K mutation: 33 subjects) were enrolled into the study. Of the patients enrolled, 89 patients were included into Cohort A (patients with no prior local therapy for brain metastases), and 83 patients were included into Cohort B (patients who received prior local therapy for brain metastases). Patients in both groups received oral dabrafenib at a dose of 150 mg twice daily. Treatment for all patients continued until disease progression, death, study treatment discontinuation, or withdrawal.

The primary endpoint, investigator-assessed confirmed OIRR (CR+PR) in patients with V600E mutation-positive melanoma, was 39% (29/74 patients) in Cohort A and 31% (20/65 patients) in Cohort B. The investigator-assessed median PFS for patients with V600E mutation-positive melanoma in Cohort A were 3.7 and 3.8 months, respectively.

The Independent Review Committee (IRC)-assessed confirmed OIRR (CR+PR) in subjects with V600E mutation-positive melanoma was 20% in Cohort A and 18% in Cohort B, which included 1 CR in Cohort A

The PFS rates were similar between Cohort A and Cohort B, and results compared favourably to other systemic treatments in this particular melanoma population. (Long 2012).

The investigator-assessed median PFS for subjects with V600E mutation-positive melanoma was 16.1 weeks in Cohort A and 16.6 weeks in Cohort B.

The IRC-assessed median PFS for subjects with V600E mutation-positive melanoma was 15.7 weeks in Cohort A and 16.0 weeks in Cohort B, similar to results observed with investigator assessment for these cohorts.

The PFS and OS rates were similar between Cohort A and Cohort B, and results compared favourably to other systemic treatments in this particular melanoma population, median overall survival from diagnosis being 17-22 weeks (Long 2012). The median OS in subjects with V600E mutation-positive melanoma was 33.1 weeks in Cohort A and 31.4 weeks in Cohort B.

BREAK-2 and BREAK-MB – safety data

The safety findings from both non-RCTs were generally consistent with the findings from BREAK-3. There were no fatal SAE's in BREAK-2 at the time of the latest data cut-off.

As might be expected from a study focussing on patients with brain metastases, the safety findings from BREAK-MB comprise neurologically-related adverse events and serious adverse events. No unexpected neurotoxicities were seen in the study. For all BREAK-MB subjects, headache (28%) was the most frequent AE regardless of causality.

A total of 73 (42%) subjects in the study died as of the clinical data cut-off date of 28 November 2011. Thirty-nine subjects died within 30 days from last dose of study treatment, and 34 subjects died >30 days from last dose. The primary cause of death was disease progression (Cohort A: 37 subjects; Cohort B: 34 subjects).

Eighty-five (49%) subjects were still under follow-up as of the last contact. With regards to fatal SAEs, three (2%) subjects in the study (two in Cohort A: Subjects 610 and 105; one in Cohort B) experienced fatal cerebral or intracranial hemorrhage. None of the three events were considered to be treatment-related and the primary cause of death for all three subjects was noted as the "disease under study".

For completeness, full safety information for BREAK-2 and BREAK-MB is provided within Appendix 10.14.

Summary of non-RCT data: BREAK-2 and BREAK-MB

The BREAK-MB study was the first and largest international prospective study of systemic therapy for $BRAF^{V600E/K}$ metastatic melanoma and brain metastases. It provided further support for the anti-tumour effect of dabrafenib in subjects with $BRAF^{V600}$ mutation. The primary endpoint was overall intracranial response rate (OIRR). The OIRR in patients with $BRAF^{V600E}$ positive metastatic melanoma was 38% (95% CI: 26.8, 49.9) and 31% (95%CI: 19.9, 43.4) for locally non-pre-treated and pre-treated patients, respectively. For the $BRAF^{V600K}$ population the OIRR was 7% (95% CI 0.2, 31.9) and 22% (95% CI 6.4, 47.6) for locally non-pre-treated and pre-treated patients.

Although the response rates were lower than the V600E population and limited by low patient numbers, the median OS for $BRAF^{V600K}$ positive tumours was consistent with data in patients with $BRAF^{V600E}$ positive tumours. Whilst further studies are required to validate the efficacy in the V600K population, the data from BREAK-2 and BREAK-MB was sufficient to support the findings from BREAK 3 and therefore warrant an indication approved by the European Medicines Agency (EMA) that was inclusive of the V600K and not limited to the V600E population.

The safety findings from BREAK-2 and BREAK-MB largely reflect the safety data demonstrated by the BREAK-3 study.

6.9 Adverse events

6.9.1 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 6.1 to 6.5 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 10.8 and 10.9, appendices 8 and 9.

BREAK- was not specifically designed to primarily evaluate differences in safety profiles of dabrafenib relative to the comparators within the scope of this appraisal. The safety data for dabrafenib from the RCTs that are relevant to the decision problem are summarised within section 6.9. The safety data for the non-RCTs is summarized in section 6.8, and described in more detail in Appendix 10.14.

6.9.2 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.

BREAK-3 – safety results

The original safety analysis in the BREAK-3 study was performed on data collected up to the cut-off date of December 19, 2011. At the December 18, 2012 cut-off date only common adverse events (AEs) and severe AEs including grade 3 and grade 4 AEs were updated. The safety data from both analyses are discussed in this section.

A comprehensive safety analysis was conducted for the randomised and crossover populations in BREAK-3.[5] The safety population included all randomised patients who received at least one dose of treatment and the crossover population included the subset of patients who were randomised to the dacarbazine arm and who elected at the point of disease progression to receive dabrafenib. Only patients who received at least one dose of dabrafenib were included in the crossover population.[5] An AE overview for the randomised phase (safety population) and the crossover populations as of December 19, 2011 is provided in Table 38.

The majority of patients received the full standard daily dosing of dabrafenib or dacarbazine through the length of the study. The mean and median daily doses of dabrafenib in the randomised phase were 284.9 mg and 300.0 mg, respectively, with a median duration on study treatment of 4.9 months. Of the 187 patients randomised to the dabrafenib arm, 49 patients (26%) had received dabrafenib for more than 6 months, as of the data cut-off of December 2011. The mean and median dose intensity of dacarbazine was 311.6 mg/m^2/week and 332 mg/m^2/week, respectively, with a median duration on study treatment of 2.8 months.[59] During the crossover phase, the mean and median daily doses of dabrafenib were 292.6 mg and 300.0 mg, respectively, with a median duration on crossover study treatment of 2.8 months.[59]

Table 38: Adverse Events Overview for the Randomised and the Crossover Phase, Dec 2011

Adverse Event (AE)	Randomised group		Crossover group
	Dabrafenib N=187)	**Dacarbazine (N=59)**	**Dabrafenib (N=28)**
Any AE, n (%)	**185 (99%)**	**54 (92%)**	**26 (93%)**
AEs related to study treatment	164 (88%)	43 (73%)	23 (82%)
AEs leading to permanent discontinuation of study treatment	5 (3%)	2 (3%)	0
AEs leading to dose reduction	34 (18%)	10 (17%)	2 (7%)
AEs leading to dose interruption/delay	51 (27%)	16 (27%)	6 (21%)
Any SAE, n (%)	**43 (23%)**	**13 (22%)**	**6 (21%)**
SAEs related to study treatment	28 (15%)	2 (3%)	4 (14%)
Fatal SAEs	1 (<1%)	0	1 (4%)
Fatal SAEs related to study treatment	0	0	0

In the randomised phase, the majority of patients in both treatment arms (99% in the dabrafenib arm and 92% in the dacarbazine arm) experienced at least one AE. In both treatment arms, a similar proportion of patients experienced AEs that resulted in treatment discontinuation, dose reductions, and dose interruptions/delays. A greater proportion of patients in the dabrafenib arm experienced treatment-related AEs and SAEs compared to dacarbazine. Most of the treatment-related AEs experienced in the dabrafenib arm were mild-to-moderate in severity. No treatment-related fatal SAEs were reported in either treatment arm. The adverse events in the randomised phase are discussed in further detail below.

In the crossover phase (at the December 2011 data cut) 26 out of 28 patients, 93% experienced AEs and 82% of AEs were considered related to dabrafenib by the investigator. No patient that reported AEs resulted in discontinuation of study treatment. SAEs were experienced by six patients (21%). These SAEs were considered related to dabrafenib by the investigator in 4 patients (14%).[59]

Randomised Phase – All Adverse Events

As of December 18, 2012, the most common AEs (≥20% of patients) with were skin-related toxic effects (hyperkeratosis, palmar-plantar papillomas), pyrexia, fatigue, arthralgia, alopecia, nausea and headache (Table 39).Each of these AEs was reported in a greater proportion of patients in the dabrafenib arm than in the dacarbazine arm.

AEs typically expected with cytotoxic chemotherapy, such as gastrointestinal symptoms (nausea, vomiting, abdominal pain) and cytopenias (including neutropenia, anaemia and thrombocytopenia) were more common in the dacarbazine arm than in the dabrafenib arm (

Table 39). Fatigue and asthenia were common (≥15%) in both arms of the study.

Table 39: Summary of All Common, Non-serious AEs Experienced by at least 5% of Patients IN BREAK-3

Adverse Event	Dabrafenib (N=187)	Dacarbazine (N=59)
Any event	183 (97.9%)	54 (91.5%)
Hyperkeratosis	73 (39.0%)	1 (1.7%)
Headache	66 (35.3%)	5 (8.5%)

Arthralgia	65 (34.8%)	1 (1.7%)
Pyrexia	57 (30.5%)	8 (13.6%)
Alopecia	54 (28.9%)	3 (5.1%)
Nausea	53 (28.3%)	30 (50.8%)
Skin papilloma	47 (25.1%)	1 (1.7%)
Fatigue	43 (23.0%)	14 (23.7%)
Palmar-plantar erythrodysaesthesia syndrome	38 (20.3%)	1 (1.7%)
Asthenia	37 (19.8%)	9 (15.3%)
Vomiting	35 (18.7%)	15 (25.4%)
Rash	35 (18.7%)	0
Back pain	30 (16.0%)	4 (6.8%)
Cough	30 (16.0%)	4 (6.8%)
Nasopharyngitis	29 (15.5%)	4 (6.8%)
Myalgia	28 (15.0%)	0
Diarrhoea	27 (14.4%)	7 (11.9%)
Constipation	26 (13.9%)	8 (13.6%)
Pain in extremity	25 (13.4%)	6 (10.2%)
Decreased appetite	22 (11.8%)	6 (10.2%)
Chills	22 (11.8%)	1 (1.7%)
Actinic keratosis	20 (10.7%)	0
Dry skin	20 (10.7%)	0
Dyspnoea	19 (10.2%)	2 (3.4%)
Erythema	18 (9.6%)	1 (1.7%)
Musculoskeletal pain	17 (9.1%)	2 (3.4%)
Ooedema peripheral	16 (8.6%)	6 (10.2%)
Seborrhoeic keratosis	16 (8.6%)	0
Skin lesion	15 (8.0%)	0
Insomnia	14 (7.5%)	2 (3.4%)
Papilloma	14 (7.5%)	0
Hyperglycaemia	13 (7.0%)	3 (5.1%)
Abdominal pain	12 (6.4%)	7 (11.9%)
Hair texture abnormal	12 (6.4%)	0
Dizziness	11 (5.9%)	3 (5.1%)
Paraesthesia	11 (5.9%)	2 (3.4%)
Melanocytic naevus	11 (5.9%)	1 (1.7%)
Acrochordon	11 (5.9%)	0
Alanine aminotransferase increased	11 (5.9%)	0
Oropharyngeal pain	10 (5.3%)	2 (3.4%)
Abdominal pain upper	10 (5.3%)	1 (1.7%)
Pruritus	10 (5.3%)	1 (1.7%)
Upper respiratory tract infection	10 (5.3%)	1 (1.7%)
Weight decreased	10 (5.3%)	1 (1.7%)
Aspartate aminotransferase increased	10 (5.3%)	0
Folliculitis	10 (5.3%)	0
Neutropenia	5 (2.7%)	10 (16.9%)
Photosensitivity reaction	5 (2.7%)	4 (6.8%)
Urinary tract infection	4 (2.1%)	4 (6.8%)
Leukopenia	3 (1.6%)	8 (13.6%)
Thrombocytopenia	3 (1.6%)	8 (13.6%)
White blood cell count decreased	2 (1.1%)	3 (5.1%)
Platelet count decreased	0	5 (8.5%)
Dyspnoea exertional	0	3 (5.1%)
Lymphocyte count decreased	0	3 (5.1%)

Cut -off Date: Dec 2012
Source: [59] Table 8.9998

Summary of Grade 3 or Grade 4 AEs

Fewer patients experienced Grade 4 AEs in the dabrafenib treatment-arm in comparison to patients treated with dacarbazine. As of December 18, 2012, Grade 4

AEs were experienced by 7 out of 187 patients (4%) randomised to the dabrafenib treatment-arm in comparison to 9 out of 59 patients (15%) in the dacarbazine treatment arm (Table 40). Each of the Grade 4 AEs reported in the dabrafenib treatment arm was reported by one patient, while in the dacarbazine treatment arm the Grade 4 AEs were reported by more than one patient.

In the dacarbazine treatment arm, fewer patients, 16 out of 59 patients (27%), experienced Grade 3 AEs compared to 72/187 patients (39%) in the dabrafenib arm (Table 40). The most common Grade 3 AEs (occurring in ≥3% of patients) in the dabrafenib arm were pyrexia (3%, 6/187 patients), back pain (4%, 8/187 patients), squamous cell carcinoma (6%, 11/187 patients), and hyperglycaemia (3%, 6/187 patients). The most common Grade 3 events on dacarbazine were neutropenia (7%, 4/59 patients), decreased appetite (3%, 2/59 patients), and leukopenia (3%, 2/59 patients) – consistent with side effects associated with chemotherapies.

Table 40: Summary of Grade 3 or Grade 4 AEs Reported by at least 2% of Patients (safety population)

Adverse Event	Dabrafenib (N=187)			Dacarbazine (N=59)		
	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Any event	72 (39%)	7 (4%)	185 (99%)	16 (27%)	9 (15%)	55 (93%)
Pyrexia	6 (3%)	0	59 (32%)	0	0	08 (14%)
Palmar-plantar eyrthrodysaesthesia syndrome	4 (2%)	0	38 (20%)	0	0	1(2%)
Asthenia	1 (<1%)	0	37 (20%)	1 (2%)	0	9 (15%)
Back pain	8 (4%)	0	31 (17%)	0	0	0
Constipation	2 (1%)	1 (<1%)	26 (14%)	0	0	1 (2%)
Decreased appetite	0	0	16 (9%)	2 (3%)	0	6 (10%)
Hyperglycaemia	6 (3%)	0	13 (7%)	0	0	3 (5%)
Abdominal pain	2 (1%)	0	13 (7%)	0	1 (2%)	8 (14%)
Anaemia	1 (<1%)	0	1 (<1%)	1 (2%)	1 (2%)	8 (14%)
Alanine aminotransferase increased	3 (2%)	0	11 (6%)	0	0	0
Hypophosphataemia	4 (2%)	0	9 (5%)	0	0	0
Squamous cell carcinoma	11 (6%)	0	11 (6%)	0	0	0
Anxiety	1 (<1%)	0	8 (4%)	1 (2%)	0	5 (8%)
Hypertension	2 (1%)	0	8 (4%)	1 (2%)	0	2 (3%)
Gamma-glutamyltransferase increased	5 (3%)	0	8 (4%)	1 (2%)	0	2 (3%)
Hepatic pain	1 (<1%)	0	3 (2%)	0	1 (2%)	1 (2%)
Squamous cell carcinoma of skin	3 (2%)	0	3 (2%)	0	0	0
Neutropenia	0	0	0	4 (7%)	4 (7%)	10 (17%)
Bone pain	0	0	1 (<1%)	1 (2%)	0	1 (2%)
Leukopenia	0	0	3 (2%)	2 (3%)	1 (2%)	8 (14%)
Thrombocytopenia	1 (<1%)	0	3 (2%)	1 (2%)	2 (3%)	8 (14%)
Fall	0	0	0	1 (2%)	0	1 (2%)
Gastrointestinal infection	0	0	1 (<1%)	1 (2%)	0	1 (2%)
Hematuria	1 (<1%)	0	1 (<1%)	1 (2%)	0	1 (2%)
Pulmonary embolism	1 (<1%)	0	1 (<1%)	1 (2%)	0	1 (2%)
Depression	0	0	0	1 (2%)	0	2 (3%)
Melena	0	0	0	1 (2%)	0	2 (3%)
Neutrophil count decreased	0	0	0	1 (2%)	0	2 (3%)
White blood cell count	0	0	0	1 (2%)	0	2 (3%)

decreased						
Angina pectoris	0	0	0	1 (2%)	0	1 (2%)
Febrile neutropenia	0	0	0	0	1 (2%)	1 (2%)
Hyperkalaemia	0	0	0	1 (2%)	0	1 (2%)
Lymphocyte count abnormal	0	0	0	1 (2%)	0	1 (2%)
Neutrophil count abnormal	0	0	0	1 (2%)	0	1 (2%)
Platelet disorder	0	0	0	1 (2%)	0	1 (2%)
Sepsis	0	0	0	1 (2%)	0	1 (2%)
Splenic rupture	0	0	0	0	1 (2%)	1 (2%)
White blood cell count abnormal	0	0	0	1 (2%)	0	3 (5%)

Data cut-off: Dec 2012

Fatal Events

No treatment-related fatal SAE occurred in either treatment arm during the randomised phase and in the crossover phase. As of December 19, 2011, one patient in the dabrafenib arm died due to elective euthanasia.[59] There was no reasonable possibility that the euthanasia was caused by dabrafenib. No other fatal SAE was reported in either arm of the study during the randomised phase or in the crossover phase.

Adverse Events of Special Interest

AEs of special interest were defined from the beginning of the dabrafenib clinical development program based upon pre-clinical observations and case reports from early clinical trials in humans.[59] Likewise, AEs that were known side effects of tyrosine kinase inhibitors or other BRAF inhibitors (e.g., vemurafenib) were monitored in all dabrafenib clinical studies in order to assess the potential for class effects. Safety findings from BREAK-3 are supplemented by the original and updated integrated summary of safety (ISS) consisting of 578 and 586 subjects, respectively, from 2 additional melanoma studies (BREAK-2 and BREAK-MB) and studies BRF113220 and BRF112680.

The updated ISS has determined the AEs of special interest to be the following:

- Pyrexia and serious non-infectious febrile events
- Cutaneous SCC and keratoacanthomas
- Other treatment-emergent malignancies (excluding cutaneous SCC, keratoacanthoma, basal cell carcinoma, and new primary melanoma)
- Palmar-plantar erythrodysaesthesia syndrome
- Renal failure
- Uveitis
- New primary malignant melanoma

Safety Conclusion

The updated ISS supporting the safety of dabrafenib monotherapy includes 586 subjects with $BRAF^{V600}$ mutation-positive melanoma who were treated at the proposed dose of 150 mg BID in 5 clinical studies. No further safety findings were

identified in the ISS report compared to the safety finding reported from BREAK-3 study.

Toxicity associated with dabrafenib therapy has been shown to be manageable and are generally of low-grade. Dose modification is not required for the majority of AE cases and permanent discontinuations due to AEs are infrequent. Treatment beyond 1 year has been demonstrated in 15% of subjects to date.

Dabrafenib safety can be differentiated from other BRAF inhibitors (vemurafenib), and chemotherapy (dacarbazine) specifically:

- The incidence of photosensitivity is low (2%) and severe dermatologic reactions (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis) have not been observed.
- High-grade elevations of liver enzymes are infrequent.
- QTcB prolongation is unusual and not of clinical significance
- There is a low incidence of clinically significant myelosuppression.

Conversely, the AE most frequently requiring dabrafenib dose modification is pyrexia, which can be successfully managed with dose interruption, dose reduction and non-steroidal anti-inflammatory drugs (NSAIDs). In conclusion, dabrafenib safety has been well-characterized in almost 600 melanoma subjects with the $BRAF^{V600}$ mutation and the risk-to-benefit in this proposed population remains favourable.

Supportive RCTs: safety data from BRF113220 & MEK115306 Combi-d study

To be consistent with the presentation of the efficacy data, the safety data for the BRF113220 and MEK115306 studies is presented as a narrative, focussing on, and supporting the use of, dabrafenib monotherapy.

When used as a monotherapy, the safety profile of dabrafenib was generally manageable. Furthermore, the number and severity of events did not appear to show any inconsistency with the findings from the BREAK-3 study, aside from hypertension and anaemia which have arisen, although in small numbers, within subjects participating in these trials. Subjects who experienced adverse events could be managed via dose interruption or reduction.

Within the BRF113220 study, only 2% of patients had to permanently discontinue therapy due to adverse events. Summaries of the adverse events are provided in Table 41 and Table 42.

Table 41: BRF113220 study overview of AEs (dabrafenib 150mg monotherapy arm; all treated population)

	Treatment Groups
Dabrafenib	**150 mg BID**
	--
N	**53 (%)**
Any AE, n (%)	**53 (100)**
Drug-related AEs	51 (96)
AEs leading to permanent discontinuation of IP	1 (2)
AEs leading to dose reduction	11 (21)
AEs leading to dose interruption	18 (34)
Any SAE[a], n (%)	**13 (25)**
SAEs leading to hospitalisation[a]	5 (9)
Drug-related SAEs	10 (19)
Fatal SAEs	0
Drug-related fatal SAEs	0

Abbreviations: BID=Two times a day; QD=Once daily.

a. In addition to the standard definition of SAEs, the protocol mandated that the following events were to be reported as SAEs, regardless of whether the subjects were hospitalized: cuSCC; LVEF decreases meeting protocol-defined stopping criteria; CSR or RVO, valvular toxicity meeting protocol-defined stopping criteria; new primary cancers; and pyrexia accompanied by hypotension and/or rigors/chills. Therefore, the total incidence of SAEs is higher than the incidence of SAEs that led to hospitalisation.

Table 42: BRF113220 study AEs experienced by ≥15% of subjects in any treatment group (dabrafenib 150mg monotherapy arm; all treated population)

	Treatment Groups
Dabrafenib	**150 mg BID**
	--
N	**53**
Any AE, n (%)	**53 (100)**
Pyrexia	14 (26)
Chills	9 (17)
Fatigue	21 (40)
Nausea	11 (21)
Vomiting	8 (15)
Diarrhoea	15 (28)
Cough	11 (21)
Headache	15 (28)
Ooedema peripheral	9 (17)
Arthralgia	18 (34)
Rash	19 (36)
Night sweats	3 (6)
Constipation	6 (11)
Decreased appetite	10 (19)
Myalgia	12 (23)
Back pain	6 (11)
Dry skin	3 (6)
Insomnia	4 (8)
Abdominal pain upper	4 (8)
Dermatitis acneiform	2 (4)
Dizziness	5 (9)
Muscle spasms	2 (4)
Pain in extremity	10 (19)
Abdominal pain	7 (13)
Actinic keratosis	5 (9)
Erythema	1 (2)
Neutropenia	1 (2)
Anaemia	3 (6)
ALT increased	1 (2)
AST increased	1 (2)
Blood ALKP increased	1 (2)
GGT increased	1 (2)
Hyperkeratosis	16 (30)
Influenza like illness	4 (8)
PPES	9 (17)
Alopecia	18 (34)
Skin papilloma	8 (15)
Pruritus generalised	8 (15)

Abbreviations: ALKP=Alkaline phosphatise; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; BID=Two times a day; GGT=Gamma-glutamyltransferase; PPES=Palmar-plantar erythrodysaesthesia syndrome; QD=Once daily.

Note: For subjects in the monotherapy arm who crossed over to combination treatment upon disease progression, only AEs with start date before the first combination dose were included in the summary.

Table 43: BRF113220 study SAEs experienced by ≥2 subjects across treatment arms (dabrafenib 150mg monotherapy arm; all treated population)

	Treatment Groups
Dabrafenib	**150 mg BID**
	--
N	**53**
Any SAE, n (%)	**13 (25)**
Pyrexia	1 (2)
Chills	1 (2)
Dehydration	0
Ejection fraction decreased	0
Pneumonia	1 (2)
Pulmonary embolism	0
Renal failure acute	0
SCC	3 (6)
Abdominal pain	1 (2)
Hyponatraemia	0
Anaemia	1 (2)
Keratoacanthoma	2 (4)
Nausea	0
SCC of skin	4 (8)
Vomiting	0

Abbreviations: BID=Two times a day; QD=Once daily.
Note: For subjects in the monotherapy arm who crossed over to combination treatment upon disease progression, only SAEs with start date before the first combination dose were included in the summary.

The Combi-d study provided a safety data set for dabrafenib monotherapy that largely reflected the findings from the other RCTs that contained dabrafenib monotherapy i.e. BREAK-3 and BRF113220. From Table 44 below, only 5% of patients discontinued treatment due to adverse events. There were no fatal SAEs. AS with the other RCTs, subjects who experienced adverse events could be managed via dose interruption or reduction.

Table 44: Overview of AEs in the Combi-d study

	Dabrafenib + Trametinib (N=209)	Dabrafenib + Placebo (N=211)
Any AE	199 (95)	203 (96)
AEs related to study treatment	179 (86)	186 (88)
AEs leading to permanent discontinuation of study treatment	19 (9)	11 (5)
AE leading to dose reduction	51 (24)	28 (13)
AE leading to dose interruption	94 (45)	63 (30)
Any SAE	73 (35)	64 (30)
SAEs related to study treatment	54 (26)	48 (23)
Fatal SAEs	4 (2)	0
Fatal SAEs related to study treatment	0	0

The most common adverse events from the Combi-d study are detailed in Table 45 below.

Table 45: Most Common AEs in (10% or More) Combination Subjects in the Combi-d study

Preferred term	Dabrafenib + trametinib (n=209)	Dabrafenib + placebo (n=211)
Any event	199 (95)	203 (96)
Pyrexia	107 (51)	59 (28)
Fatigue	74 (35)	74 (35)
Headache	63 (30)	62 (29)
Nausea	63 (30)	54 (26)
Chills	62 (30)	33 (16)
Arthralgia	51 (24)	58 (27)
Diarrhoea	51 (24)	30 (14)
Rash	48 (23)	46 (22)
Hypertension	46 (22)	29 (14)
Vomiting	42 (20)	29 (14)
Cough	34 (16)	35 (17)
Pain in extremity	30 (14)	33 (16)
Oedema peripheral	30 (14)	10 (5)
Decreased appetite	23 (11)	25 (12)
Myalgia	22 (11)	24 (11)
Constipation	22 (11)	18 (9)
Abdominal pain	22 (11)	14 (7)
Alanine aminotransferase increased	22 (11)	10 (5)
Aspartate aminotransferase increased	22 (11)	7 (3)
Asthenia	20 (10)	27 (13)
Nasopharyngitis	20 (10)	15 (7)
Dizziness	20 (10)	12 (6)

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

6.9.3.1 Safety overview from clinical studies involving dabrafenib (BREAK-3, BRF113220, Combi-d, BREAK-2 and BREAK-MB)

Dabrafenib has been shown to have a manageable safety profile. Photosensitivity is a notable side effect with vemurafenib seen in the BRIM-3 study, and this can have a significant effect on quality of life,[81-83] but was not common with dabrafenib monotherapy in BREAK-3 or within the dabrafenib monotherapy arms of BRF113220 or Combi-d.

Dabrafenib monotherapy shares some adverse events with vemurafenib e.g. nausea, vomiting. However there are some events that are particularly associated with dabrafenib. Pyrexia was common with dabrafenib (although only 3% of patients had a Grade 3 event).[5] In BREAK-3, treatment with dabrafenib was well tolerated with the majority of AEs being mild-to-moderate in severity. There were few treatment discontinuations due to AEs; 3% in each of the treatment arms. Mortality rates were similar with both treatments; 11% of patients in the dabrafenib group and 14% of patients treated with dacarbazine, and all of these deaths were due to disease progression except one patient who chose elective euthanasia.[5,9]

The most common AEs (≥20%) in the dabrafenib arm were hyperkeratosis, headache, pyrexia, arthralgia, skin papilloma, alopecia, and PPE syndrome. In the dacarbazine arm, the most common AEs included nausea, vomiting, and fatigue, as is consistent with cytotoxic chemotherapies. Most patients who experienced a dose reduction or interruption due to toxicities were able to continue treatment with dabrafenib or dacarbazine following dose reduction or resolution of the events.

There was a similar rate of SAEs in both treatment groups (23% and 22% with dabrafenib and dacarbazine, respectively). Serious AEs reported in more than 1% of patients in the dabrafenib arm were pyrexia, cuSCC and new primary malignant melanoma. Events of cuSCC and new primary malignant melanoma were manageable and did not result in treatment discontinuation. Among patients treated with dabrafenib, 6% experienced cuSCC and 3% developed keratoacanthomas. This is comparable to the occurrence of cuSCC and keratoacanthomas in the BREAK-2 study[57], and with vemurafenib.[38].

Conclusion

All patients receiving the newer, targeted agents (dabrafenib or vemurafenib) will require regular monitoring, in particular for the development of secondary squamous cell carcinomas (SCC) and other skin lesions and dermatological reactions, and for ophthalmological complications.[76,84,85]

Pyrexia is a recognised toxicity associated with dabrafenib and was shown in clinical trials to become more frequent and more severe when dabrafenib was used in combination with trametinib, although it remained generally manageable with antipyretic agents.[7,85] However, the incidence and severity of phototoxicity, a vemurafenib-associated adverse event, is numerically lower with dabrafenib.

Resource requirements for routine monitoring of patients may therefore vary somewhat in relation to the different adverse event profiles of dabrafenib and vemurafenib, although monitoring requirements are unlikely to be materially different between these treatments.[76,84,85] It is likely therefore that the use of dabrafenib for $BRAF^{V600}$ mutation-positive metastatic melanoma would have no significant additional impact on health services compared to that required for effective use of vemurafenib.

6.10 Interpretation of clinical evidence

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

Dacarbazine was, until relatively recently, the standard of care for the treatment of metastatic melanoma. Vemurafenib (Roche Products Ltd) was the first licensed selective BRAF inhibitor for V600 metastatic melanoma. It was recommended by NICE as an option for treating $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma in December 2012. It has since superseded dacarbazine as the standard of care for the treatment of this disease. The efficacy of dabrafenib versus both comparators (dacarbazine and vemurafenib) is discussed below in turn.

Versus dacarbazine

Dabrafenib has shown significantly improved efficacy compared to dacarbazine in the BREAK-3 study.[5] Following the updated analysis of the most mature data cut (25 June 2012), the primary endpoint, median PFS was 6.9 months for dabrafenib compared to 2.7 months for dacarbazine with a statistically significant reduction in the relative risk for progression or death of 63%. Similarly, objective response rates were improved for dabrafenib versus dacarbazine (59% versus 24%).[9] Median overall survival of dabrafenib was also improved versus dacarbazine (18.2 months versus 15.6 months) but this was not statistically significant, as is evidenced by the wide confidence intervals. This 2.6 month survival gain was associated with an ITT hazard ratio of 0.76 (95% CI: 0.48-1.21), that has not been adjusted for crossover. Once there is adjustment for crossover, this yielded a hazard ratio of 0.55 (95% CI 0.21, 1.43).

There are several possible reasons underlying the lack of significance in the overall survival estimates. In part, this may be due to the immaturity of the overall survival dataset and the relatively small patient numbers in the control arms due to the 3:1 randomisation. However, the greatest contributing factor is likely to be the level of crossover (57%) of patients to the investigational treatment arm within BREAK-3 (see Table 13). Adjustment for this crossover using the RPSFT methodology generally improves the hazard ratios from ITT results, although the confidence intervals remain wide because the RPSFT method utilises the p-value from the ITT population.

Versus vemurafenib

The median PFS for dabrafenib is the same (6.9 months) as that for vemurafenib in numerical terms (data cut-offs: June 2012 for BREAK-3, February 2012 for BRIM-3).[5,6,37,38] The ITC (see Table 36) for PFS suggests that there is no significant difference between dabrafenib and vemurafenib (HR 0.97, (95% CI: 0.59, 1.60). Equally, the objective response rates for dabrafenib and vemurafenib are similar at their latest data cut-off; 59% (June 2012 data cut-off) and 57% (February 2012 data cut-off), respectively, although the level of maturity may differ between BREAK-3 and BRIM-3.[5,6,37,38] The dacarbazine arm for BREAK-3 demonstrated an objective response rate of 24% compared to 5.5% in BRIM-3.[84] The latter figure is more in line with historical data for dacarbazine.[37] It is possible that the relatively small patient population in the dacarbazine cohort in BREAK-3 has, due to the effects of chance,

led to a higher than expected response rate, since smaller cohorts are more likely to be affected by individual patient outliers than larger cohorts.

Median overall survival in BREAK-3 for dabrafenib is higher in numerical terms, but not significantly different compared to dacarbazine (18.2 months versus 15.6 months; HR 0.76, 95% CI 0.49, 1.18)[6], while the median overall survival for vemurafenib in BRIM-3 at the latest data cut-off was 13.6 months versus 10.3 months for dacarbazine, with a hazard ratio of 0.76 (95% CI: 0.63, 0.93; p< 0.01).[38] OS results from both BREAK-3 and BRIM-3 were confounded by the dilution of treatment effect which occurs as a result of crossover of patients allocated to the control arm to active treatment at the time of disease progression. However the extent of this confounding differed due to the different time points at which patients in each control arm were permitted to crossover to active therapy. BRIM-3 permitted patient crossover only as a result of a protocol amendment at the time of the planned interim analysis (December 2010) while BREAK-3 permitted crossover from the study start. As a result a greater number of patients crossed over to dabrafenib from dacarbazine in BREAK-3 than crossed over to vemurafenib in BRIM-3 at every datacut, see Table 13 and Table 33.

The results of the ITC for the PFS and OS of dabrafenib versus vemurafenib are detailed in Table 36 and Table 37 respectively. The analyses utilised crossover adjusted HRs for overall survival for each study and the results suggest that there is no evidence of a difference between dabrafenib and vemurafenib, despite the wide confidence intervals (OS HR 0.86, 95% CI 0.32, 2.29). As explained previously, these may be due to the immaturity of the data sets, as well as methodological issues pertaining to the RPSFT method.

The adjusted median OS for dabrafenib within the Phase II BRF113220 study was 448 days or 14.7 months. This provides a more robust estimate of the overall survival benefit of dabrafenib, and this is comparable with the unadjusted median OS for vemurafenib from BRIM-3 of 13.6 months.

Safety of dabrafenib

Versus dacarbazine

In BREAK-3, the most common AEs (≥20%) related to dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, skin papilloma, alopecia, and PPE syndrome.[76] Overall, there were few all-grade and Grade 3/4 adverse events seen with dabrafenib and dacarbazine.[5] Of note, 7% of patients experienced Grade 4 neutropenia with dacarbazine and no cases among dabrafenib-treated patients. Grade 3 pyrexia and Grade 3 squamous cell carcinoma/keratoacanthoma was found in 3% and 4% respectively of dabrafenib patients, with no cases among dacarbazine patients. In BREAK-3, 7% of patients receiving dacarbazine experienced photosensitivity. All of these events were Grade 1. In the dabrafenib arm, 5 (3%) patients experienced photosensitivity; three (2%) were Grade 1, and two (around 1%) were Grade 2.[5]

Versus vemurafenib

Although there are no head-to-head data, dabrafenib appears to be associated with less phototoxicity than vemurafenib; 3% Grade 1-2 photosensitivity in the BREAK-3

study[5], compared with 33% all-grade events for photosensitivity with vemurafenib, 3% of which were Grade 3 (updated safety analysis, March 2011).[79]

Additionally, certain types of hyperproliferative skin toxicities appear to be more common and more severe with vemurafenib than with dabrafenib. In BRIM-3, for vemurafenib there were 17% all-grade cutaneous SCC (16% Grade 3), 9% keratoacanthomas (all of which were Grade 3 events). By contrast in BREAK-3, 4% of patients receiving dabrafenib had Grade 3 cuSCC/keratoacanthoma (2% Grade 2 events).[5,79] Whilst such a comparison is not ideal in the absence of head-to-head data, it may be reasonable to suggest that dabrafenib is associated with fewer skin toxicities than vemurafenib.

Arthralgia was more common with vemurafenib (53% all-grade; n=178, 4% Grade 3; n=13)[79] than with dabrafenib (19% all-grade; n=36, 1% Grade 3; n=2).[9] Treatment-related pyrexia was reported with dabrafenib (16% all-grade; n=30, 3% Grade 3; n=5), while for vemurafenib there was 18% all grade pyrexia, but no cases of Grade 2 or above were reported.[9] Hyperkeratosis was more common with dabrafenib (36% all-grade; n=67, 1% Grade 3; n=2) versus vemurafenib (24% all-grade; n=81, 1% Grade 3; n=3)[9], as well as palmar-plantar erythrodysaesthesia syndrome; dabrafenib (20% all-grade; n=37, 2% Grade 3; n=4) versus vemurafenib (8% all-grade; n=27, <1% Grade 3).

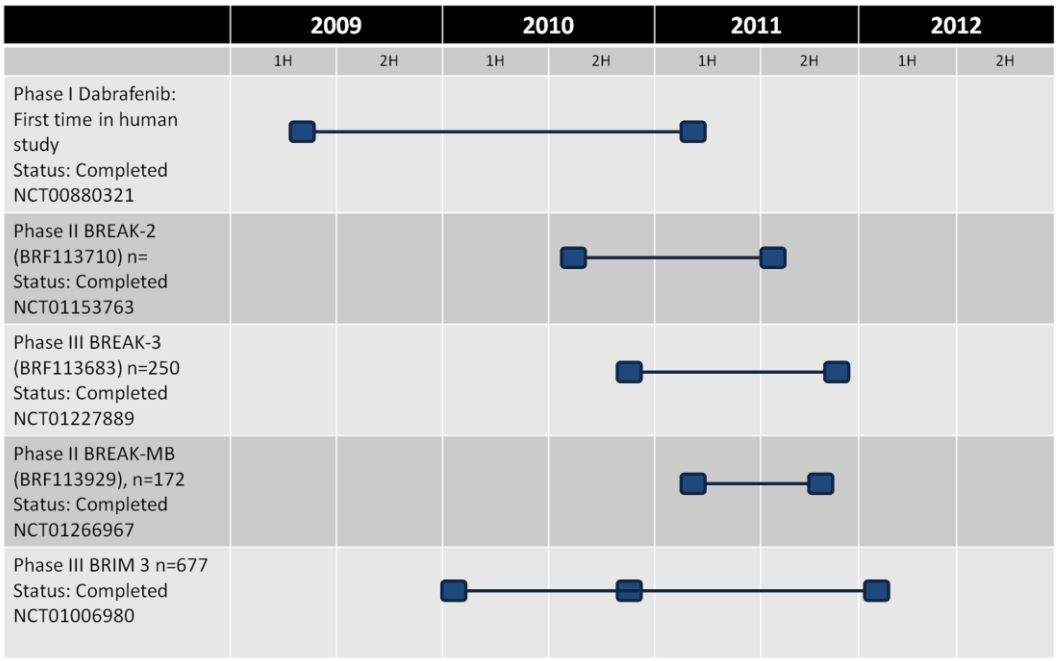
Issues around study design

To help with assessing and contextualising the efficacy and safety data for dabrafenib, it might be useful to consider various aspects associated with the study design of the GSK development programme, including:

- Timelines for the GSK Phase II and III development programme
- Allowance for crossover of patients allocated to the control arm to receive active treatment upon independently-confirmed disease progression, and the confounding effect on overall survival
- The value of PFS as a true measurement of the efficacy of a treatment

Timelines for the GSK clinical development programme for dabrafenib

The development programme for dabrafenib as well as the Phase 3 programme for vemurafenib (BRIM-3) are illustrated in the figure below. These timelines demonstrate that dabrafenib was developed almost in parallel with vemurafenib, representative of the rapid increase in understanding of the molecular biology of melanoma. The aim of such a programme was to deliver further treatment options for patients as quickly as possible, which may not have happened had a traditional sequential Phase I to III approach been adopted for dabrafenib.



Start of study/primary efficacy endpoint

n.b. BRIM-3 had a revised co-primary endpoint of PFS and OS following a protocol amendment in October 2010. Median PFS was reached in December 2010, median OS was reached in February 2012, and presented at the American Society of Clinical Oncology, Chicago, in June 2012.

Figure 11. Summary of timelines for the dabrafenib clinical development programme discussed in this submission alongside BRIM-3

The timeline of the dabrafenib clinical development programme had a bearing on the choice of comparator for these intervention trials. Prior to the availability of targeted therapies (such as vemurafenib and dabrafenib), cytotoxic chemotherapy (such as dacarbazine or paclitaxel) was used to treat metastatic melanoma. Dacarbazine was historically associated with a low response rate of 7 to 12% and a median overall survival of 5.6 to 7.8 months after the initiation of treatment.[37] Being the only chemotherapy licensed for the treatment of metastatic melanoma, dacarbazine was the most suitable comparator for vemurafenib at the time of the BRIM-3 study. Likewise, dacarbazine was a valid comparator for the BREAK-3 study since vermurafenib was still an investigational agent at this point.

Early results of the trials that utilised dacarbazine as the comparator demonstrated a clear benefit for giving patients the opportunity to receive a BRAF inhibitor. At the time of the planning and start of the BREAK-3 study, vemurafenib had not yet been licensed, nor become the standard of therapy worldwide, so was not considered as a relevant comparator. Therefore dacarbazine was the only suitable comparator.

Allowance of crossover of patients from the control arm to the treatment arm

The BREAK-3, BRF113220 and BRIM-3 studies all allowed patients initially randomised to the control arm to crossover to receive the investigational treatment upon independently-confirmed disease progression.[5,7,37,86] As previously described, where crossover was allowed the survival advantage conferred by the investigational agent is likely to be underestimated since patients in both arms of the study will have had the opportunity to benefit from the investigational treatment at some point during

the study. Crossover is likely to have had a more profound effect in BREAK-3 as this was permitted from the study inception (as opposed to following an interim analysis, as in BRIM-3; see Section 6.7).

The optimal method to adjust for the confounding effects of crossover remains an area of academic debate. The Rank Preserving Structural Failure Time model (RPSFT) was considered most appropriate for the datasets and the sample sizes being evaluated – Refer to Table 26 for the results of this adjustment. This confounding also affected the BRIM-3 study and the manufacturer submitted adjusted survival estimates to NICE which were later used as inputs in modelling for the purposes of the vemurafenib appraisal.

It is clear that, wherever patients initially randomised to control are provided the opportunity to benefit to any extent from the investigational intervention, some bias will exist whereby any difference between the 'estimated' treatment effect and the 'true' treatment effect that would have been observed had there been no treatment crossover, will need to be considered, and adjusted for, if there are to be appropriate resource allocation decisions being made.[87]

The value of PFS as a true measurement of the efficacy of a treatment

An important question is whether oncologists and NICE should accept PFS as a surrogate for OS. With a fast evolving treatment landscape, it is becoming very difficult to conduct well-powered, randomised studies in metastatic melanoma using comparators that potentially disadvantage those patients who receive them. Therefore, allowance within protocols for crossover to the intervention under consideration is increasingly becoming the norm. This usually leads to confounding of overall survival results because crossover is often permitted upon progression. In such cases the PFS endpoint is not diluted by the effects of post-progression treatment following crossover.

In addition to the statistical methologies being used to adjust for the confounding effect of treatment crossover on OS, work has been done to validate PFS as a surrogate marker of OS via a meta-analysis of 10 randomised controlled trials enrolling 4,215 metastatic melanoma patients.[78] The analysis performed by Flaherty et al is discussed in Appendix **Error! Reference source not found.** and has shown a significant correlation between PFS and OS in metastatic melanoma, regardless of the impact of crossover. Despite some evidence of a weakening of the correlation in the case of more mature data with increased crossover (more than 50%), the authors concluded that PFS is a robust surrogate marker for OS. This should help to add to the body of evidence supporting the use of dabrafenib monotherapy.

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

Table 46. Summary of the strengths and limitations of the clinical-evidence base for dabrafenib (BREAK-3)

Strengths of clinical evidence base	Weaknesses of clinical evidence base
Randomised, controlled study showing improved response rates, time to	This was an open-label study. However any negative effect due to the possible

response, progression-free survival with dabrafenib compared to the standard of care at the time of the study, dacarbazine.	introduction of bias has been lessened by including a blinded, Independent Review Committee to assess progression.
The similar design of BREAK-3 to BRIM-3 meant that a robust ITC between dabrafenib and vemurafenib was possible and this demonstrates broad similarity in terms of efficacy. As stated above, dacarbazine was chosen as the comparator as it was the standard of care at the time of the study.	The current standard of care, vemurafenib, was not used as a comparator, as it was not licensed (and was not an established standard of care) at the time that this study was designed and conducted.
The response rates and time to response show significant improvement compared to that found with dacarbazine	The overall survival was confounded by the crossover which was allowed upon progression, as confirmed by independent radiologic assessment.
	In BREAK-3, the independent- and investigator-assessment for response rates and time to response for dacarbazine appeared to show some discordance (response rates: 6% vs 19% respectively; time to response 12 vs 6.6 weeks respectively).

6.10.3 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 field of melanoma has seen significant advances in treatments and consequently outcomes for patients in the last four years. It took over a decade for similar progress to be seen for patients with breast and colorectal cancer. However, patients with metastatic melanoma have a short life expectancy and there is an ongoing need for improved treatments. The trials discussed here provide relevant evidence for this patient group.

6.10.3.1 Clinical outcome measures in the clinical trials

The primary and secondary endpoints, used to demonstrate the efficacy and safety of dabrafenib are all well established measures of efficacy in oncology, and have been utilised in the development of many existing licensed therapies. These outcomes are familiar to oncologists, and are relevant to patients with metastatic melanoma, and have been accepted by NICE in the context of other appraisals of cancer therapies.

Due to the unavoidable impact of crossover, OS data used to support this submission is confounded. Adjustments to the raw OS data have been made using a respected

methodology which will be familiar to NICE. Along with PFS:OS correlation analysis, [7,78] this strongly supports the conclusion that dabrafenib confers a substantial survival benefit over that of dacarbazine for patients with metastatic melanoma.

Despite the lack of head-to-head comparisons between dabrafenib and vemurafenib, robust ITCs have been conducted. The studies of interest reported similar outcomes, and their comparable designs and patient inclusion have enabled analyses that provide potentially clinically meaningful comparative evidence. Taken together, this has allowed GSK to model the relative efficacies of the two interventions.

6.10.3.2 Patient population and treatment pathway used in BREAK-3,

Generalisability of the trials to clinical practice in the UK is discussed more fully in Section 6.10.4.

Evaluation of the patient demographic data for all studies in Section 6.3.4 suggests that the trial patients are representative of unresectable/metastatic BRAF^{V600} mutation-positive melanoma patients who would be eligible for treatment in the UK. Patients must be identified as having the BRAF^{V600} mutation and BRAF testing is now routine and widespread in this country. While the BREAK-3 trial was not conducted in the UK, there is no reason to expect that geographical differences would render the results of this trial inapplicable to UK BRAF^{V600} mutation-positive metastatic melanoma patients.[59]

In general, patients in BREAK-3 were treated in a manner that is reflective of clinical practice and the way in which the treatments will likely be used in the UK, as discussed further below in section 6.10.4. This is confirmed by an analysis of the study protocols and melanoma treatment guidelines including those presented by the British Association of Dermatologists (BAD)[††] and the National Comprehensive Cancer Network (NCCN)[‡‡].

6.10.4 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?

No major factors were identified as limiting the external validity of the clinical data that supports the use of dabrafenib.

Dabrafenib received a marketing authorisation from the EMA as a monotherapy for the treatment of unresectable/metastatic BRAF^{V600} mutation-positive metastatic melanoma. Patients participating in the underlying BREAK-3 clinical study were treatment-naive in the advanced metastatic-melanoma setting. The appraisal therefore focuses on unresectable/metastatic BRAF^{V600} mutation-positive metastatic

[††] BAD: http://www.bad.org.uk/Portals/_Bad/Guidelines/ClinicalGuidelines/Melanomaguidelines2010.pdf
[‡‡] NCCN: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#melanoma

melanoma patients who have received no prior therapy to whom the trial results are entirely generalisable.

BREAK-3 was a multi-national trial with 250 patients enrolled from 12 countries, across the U.S., European Union, Canada, Russian Federation and Australia. Unlike BRIM-3, no UK centres were involved with the BREAK-3 study. It is not unexpected that participation of UK trial centres was limited given the small underlying population with $BRAF^{V600}$ mutation-positive metastatic melanoma relative to other cancer populations. Importantly however, there are no identified reasons, nor are there likely to be any unidentified reasons, why any geographical differences would render the results of these studies inapplicable in England and Wales. The demographic and disease characteristics of participant patients in the BREAK-3 study are similar to those described in BRIM-3, and are representative of patients with advanced/metastatic melanoma in the UK.

The study populations were selected for the trials using BRAF testing, which allowed for the identification of the appropriate patient for the targeted therapies under investigation. This method of patient identification is not new and is routinely used in the assessment of patients with metastatic melanoma in the UK.

Study treatment was initiated at the full licensed dose, in line with the marketing authorisation for dabrafenib. The dose may be, and indeed was, modified during the trial to deal with adverse events, as described in 6.9.2.1.2, consistent with the way that the drug will be utilised in clinical practice. Subjects received full supportive care during the trial, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrhoeals, and analgesics, and other care as deemed appropriate, in accordance with their institutional guidelines. It is highly likely that patients eligible for dabrafenib in clinical practice will require similar concomitant medications for the management of co-morbid conditions, infections and other therapy or disease-related complications.

In summary, there is no reason to believe that the clinical benefits of dabrafenib seen in BREAK-3, would not be applicable to the patients eligible to receive dabrafenib in UK clinical practice.

7 Cost-effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 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 10.10, appendix 10.

A broad range of economic studies were identified through a systematic review of the economic literature which focussed on treatments for metastatic melanoma (initial search in April 2012, updated in October 2013). Details of the search strategy for this review (which was conducted alongside the review for quality of life literature) are provided in Appendix 1**Error! Reference source not found.**.15.

The review reported on cost-effectiveness analyses, direct cost studies and medical resource use/burden of illness studies. Only those studies reporting results of relevance to this decision problem were considered relevant for discussion below. A critical appraisal of included studies is provided in Appendix **Error! Reference source not found.** and a table of excluded studies is provided at the end of this section.

Description of identified studies

7.1.2 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.

Nine cost-effectiveness studies met the inclusion criteria for the systematic review of economic literature,[88-97] only one of which is deemed relevant for discussion here.[94] Reasons for exclusion from discussion in this appraisal are detailed in Table 47. Alva 2012 refers to the NICE submission of vemurafenib for BRAF^{V600} mutation-positive metastatic melanoma patients. This NICE submission was also found through the CRD search for relevant technology appraisals and the summary below relies on the additional detail provided through the manufacturers' submission to NICE and the associated critique.[40,41,94]

Vemurafenib is positioned as a key comparator in this appraisal and given its identical indication to the population in this decision problem, the details of the manufacturer's submission to NICE are of particular relevance. A detailed discussion of this cost-effectiveness analysis and its critique is provided in Appendix **Error! Reference source not found.**.

Vemurafenib for patients with BRAF^{V600} mutation-positive metastatic melanoma – NICE submission [40,94]

A three-state partitioned survival model was developed by the manufacturer to investigate the cost-effectiveness of vemurafenib as a first line treatment of BRAF^{V600} mutation-positive melanoma versus dacarbazine. The model included three distinct health states: progression-free survival, progressed disease, and death and assessed outcomes over a 30-year time horizon (equivalent to a lifetime horizon) from an England/Wales NHS PSS perspective. Baseline efficacy data were from a phase III randomised, open-label study comparing vemurafenib to dacarbazine (BRIM-3). Utilities in the model were sourced from literature[98] and weighted by response rate to distinguish quality of life in patients achieving a response to treatment from that of patients with stable disease. Non-differential discounting was applied at 3.5% per annum and a wide range of costs were incorporated into the model, including drug costs, cost of administration, AE costs and post-progression supportive care costs. Deterministic and probabilistic sensitivity analyses determined that the ICER was most sensitive to long term projections of OS and the post-progression utility values used.

An exponential function was fitted to the Kaplan-Meier data to extrapolate PFS for both the vemurafenib and dacarbazine arms beyond the study end. Extrapolation of OS data was also necessary as a large number of BRIM-3 patients had not experienced an event by the March 2011 data cut. While parametric extrapolation, often with a single parametric function, is common in CEA models in oncology, this was the second appraisal to deem this approach inappropriate (the first being the appraisal of ipilimumab for previously treated patients with metastatic melanoma). A more complex stepwise approach to modelling OS was therefore employed in the vemurafenib assessment to ensure face validity of the model and comparability with historical data in patients with advanced melanoma.

Vemurafenib was approved by NICE for the treatment of locally advanced or metastatic BRAF^{V600} mutation-positive malignant melanoma in December 2012. The Committee concluded that the ICER for vemurafenib compared with dacarbazine ranged between £44,000 and £51,800 and was satisfied that vemurafenib met all the criteria for being a life-extending, end of life treatment.[40]

A detailed summary of this appraisal is provided in Appendix **Error! Reference source not found.** and the details of the vemurafenib model and the discussion that ensued between the manufacturer, the ERG and the NICE committee throughout three appraisal committee meetings is relevant to the consideration of the approach to modelling in this appraisal.

Table 47 below describes the other studies of cost-effectiveness identified in the systematic review and highlights the reason for exclusion from discussion here.

Table 47. Summary list of other cost-effectiveness evaluations

Reference	Model	Intervention	Population and perspective	Result	Comment

Cormier 2007 [92]	Probabilistic Markov model over lifetime horizon	Adjuvant high-dose interferon alfa (HDI) treatment (versus no HDI treatment)	US patients with high-risk melanoma from a third party payer's perspective	Base case (50yo, stage III melanoma): incremental cost $48,129 and 0.56 QALY gains; ICER = $85,776/QALY	Not relevant due to comparator and perspective
Hirst 2012 [91]	Decision-analytic model	Sunscreen promotion (daily use vs. discretionary use) for protection against melanoma	Skin cancer in Australians from Australian health care perspective	Discounted incremental cost/QALY ('daily' use of sunscreen vs. 'discretionary' use) = AU $42,600	Intervention not relevant; perspective not relevant; population (prevention)
Morton et al. 2009 [90]	Markov model over 20 year horizon	Wide excision (WEX) and sentinel node biopsy (SNB) compared to WEX only	Primary melanomas (>1mm thickness) from an Australian health system perspective	ICER of AU $1,983/QALY suggested that WEX + SNB offers an improvement in health outcomes with only a marginal cost increase	Intervention not relevant, population not relevant (not metastatic), perspective not relevant
Dixon (2006) [88]	CEA based on randomised controlled trial	Low dose extended duration adjuvant interferon alpha-2a (IFN α-2a) vs placebo	Patients with malignant melanoma over a 5 year time horizon	ICER of £41,432 at 5 years; IFN α-2a unlikely to be CE treatment option for malignant melanoma in the UK (at £30 000/QALY threshold)	Intervention not relevant, population not limited to metastatic melanoma
Hillner et al. 2000 [89]	Unclear	Temozolomide (TEM) vs. single agent intravenous (IV) dacarbazine	US societal perspective	Resultant ICER was $36,990/life year gained	Population is relevant however intervention not relevant, perspective not relevant; model structure unclear
Lee et al, 2012 [93] and Diaz et al, 2012[96]	Semi-Markov model with piecewise approach to modelling OS	Ipilimumab vs BSC	Previously treated metastatic melanoma patients from a UK	Resultant ICER was £65,303/QALY	Population is not relevant to the decision problem; intervention is not a

			perspective		comparator for previously untreated patients
Radford et al, 2013[95]	Three-state Markov model with efficacy data from pivotal trial of ipilimumab in previously untreated patients	Ipilimumab vs BSC	Patients with metastatic melanoma from Portuguese perspective over a lifetime horizon	Resultant ICER was €53,579/LYG	Intervention is not a comparator in this appraisal
Barzey et al, 2013[97]	Three-state Markov model	Ipilimumab vs. BSC	Previously-treated metastatic melanoma patients over a lifetime horizon; from a US perspective	Resultant ICER was $128,656/QALY	Ipilimumab is not a comparator in this appraisal

Summary

The cost-effectiveness study described here relates to an important new treatment for metastatic melanoma patients, vemurafenib. This treatment is directly relevant to this decision problem as it is the key comparator for dabrafenib.

7.1.3 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)§§ or Philips et al. (2004)***. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

A quality assessment for the cost-utility assessment of vemurafenib versus dacarbazine is presented in Appendix **Error! Reference source not found.**.

§§ 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.

*** 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.

7.2 De novo analysis

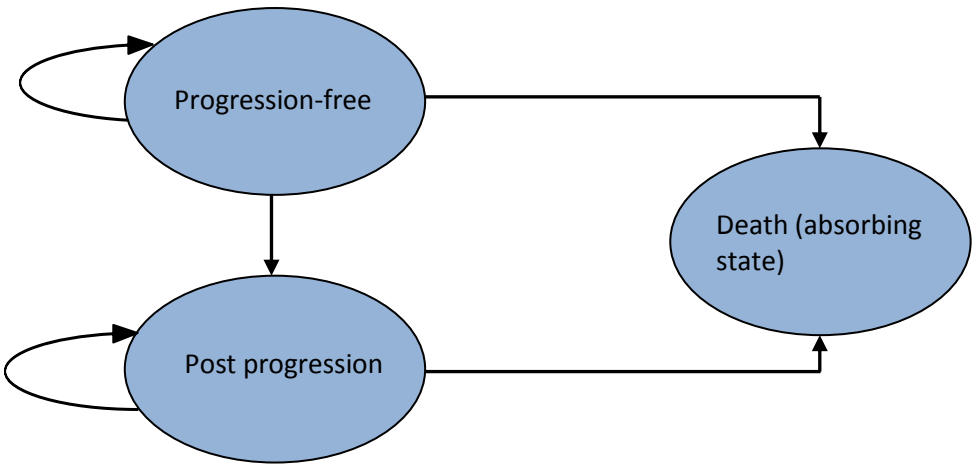
Patients

7.2.1 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 1.3 and 6.3.3, 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 economic evaluation includes previously untreated adult patients with $BRAF^{V600}$ mutant metastatic melanoma. There are insufficient clinical data with which to construct an economic case for previously treated (second-line) patients. A focus on frontline patients is consistent with the clinical evidence and is a comparable approach to that taken by the manufacturer in the NICE submission for vemurafenib.

Model structure

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



A partitioned survival model characterised by three mutually exclusive health states ("alive progression-free", "alive and progressed" and "death") was developed to estimate lifetime outcomes and costs of patients with metastatic melanoma assumed to receive treatment with dabrafenib or with its comparator treatments (vemurafenib and dacarbazine).

The proportion of patients in each health state over time is estimated based on survival functions for progression-free survival (PFS) and overall survival (OS). The starting point for the evaluation is the empirical data from the BREAK-3 study.

In the absence of head-to-head data, the base case utilises the results of the indirect treatment comparison of dabrafenib versus vemurafenib (see Section 7.3) to

generate PFS and OS curves for vemurafenib. The impact of assuming a class effect is explored in a sensitivity analysis, i.e. assuming that PFS and OS for vemurafenib are the same as for dabrafenib (see Section 6.7 for the rationale behind this).

Costs and quality of life depend on treatment received and the expected time in the health states. For each therapy, expected PFS is calculated as the area under the curve (AUC) for the PFS distribution. Expected OS is calculated as AUC for the OS distribution. Expected PPS is calculated as the area between the PFS and OS curves or the difference between expected PFS and expected OS.

Incremental cost-effectiveness ratios (ICERs) are expressed in terms of the cost per quality adjusted life years (QALYs) gained. The base case employs a 30-year year time horizon approximating a lifetime projection. Future costs and QALYs are discounted at a 3.5% annual rate.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Patients with metastatic melanoma may experience changes in their quality of life which correspond to the progressive health states that are a feature of this disease. Progression is a key determinant of quality of life[99,100] and in the case of many cancer therapies, a marker of treatment failure, and therefore cessation. It is reasonable to structure a model on the basis of the distinct health states associated with the disease and to separate out progression from pre-progression as this allows the differences in treatment costs, management and patient experience during these discrete periods to be reflected. The same applies to the incorporation of a death state.

Partitioned survival modelling is one of two broad approaches (the other being Markov modelling) commonly taken in cost-effectiveness modelling to represent the patient's journey. They are not uncommon in HTAs of oncology medicines and have been used in numerous prior evaluations of the cost-effectiveness of targeted therapies for advanced or metastatic cancer[101] including the recent evaluation of the cost-effectiveness of vemurafenib in BRAF mutation-positive patients,[40] as well as others.[102,103]

A partitioned survival analysis was considered a more appropriate design than a Markov model in this case and whilst they are similar, the decision was driven by their key differences. This model takes as inputs the survival distributions for PFS and OS whereas a Markov model requires the distributions of PFS and PPS. PPS distributions are often not available for comparator trials. The use of the partitioned survival model ensures that the model results for OS match those observed in the trial for the duration of the trial. While it is of course possible to calibrate the distributions of PPS for each treatment arm in a Markov model to yield estimates of the distributions of OS observed in the trial, the additional value of such an approach is uncertain. Additionally, whereas the partitioned survival model allows the application of HRs for OS from ITCs for therapies not examined in the trial, a Markov cohort approach requires HRs for PPS, and again, these are rarely, if ever, reported. For these reasons, and to be consistent with the methods used in prior evaluations of the cost-effectiveness of vemurafenib and ipilimumab in metastatic melanoma, a partitioned survival analysis was used in this evaluation.

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

The modelled health states capture differences in the costs and quality of life of patients pre- and post-progression. Disease progression is assumed to be a key determinant of quality of life and medical resource utilisation. The model assumes that dabrafenib is administered until disease progression or death (if occurring prior to progression). When therapy is initiated, patients are assumed to be in the “alive pre-progression” health state and are at risk of disease progression and/or death over time. Patients who progress are assumed to discontinue therapy and those who discontinue are assumed to transition to the “alive and progressed” health state and to stay in that state until death.

7.2.5 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.

Patients with metastatic melanoma have, until recently, had a very poor prognosis. Even with the introduction of vemurafenib – the first drug in the class of BRAF inhibitors – there is still a significant unmet need for patients and survival and quality of life are important patient outcomes. The economic model in this assessment captures both of these endpoints. As described in Section 2, the economic burden of treating metastatic melanoma is high and the model incorporates the costs accrued by patients in the different health states they experience during their disease. Duration of treatment reflects underlying disease progression because the drugs are usually continued until patients are no longer receiving benefit (or unacceptable toxicity).

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

Additional key features of the model are described in Table 48 below.

Table 48. Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (30 years)	30-year time horizon is a reasonable representation of the lifetime for patients in the model (mean age 53 years)	NICE 2013[65]
Cycle length	One week	To permit consideration of therapies with different cycle durations (e.g., one, two, three, or four weeks) and to eliminate the need for a half-cycle correction.	
Half-cycle correction	None	Not required (see above)	
Were health effects measured in QALYs; if not, what was used?	Yes	As per reference case	NICE 2013[65]
Discount of 3.5% for utilities and costs	Yes	As per reference case	NICE 2013[65]
Perspective (NHS/PSS)	NHS	As per reference case	NICE 2013[65]
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 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?

Dabrafenib and its comparators are implemented in the model as per their current/anticipated marketing authorisations and doses.

7.2.8 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.

No clinical stopping rule is implemented in the model. Patients are treated until progression and average treatment duration reflects actual trial experience (implemented in the model by the application of a relative dose intensity (RDI) multiplier as derived from the results of the interventional trials).

7.3 Clinical parameters and variables

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

As described in Section 7.2.2, empirical data from the BREAK-3 study are the starting point for the economic model. Modelled PFS and OS survival distributions were segmented into: 1) the trial segment; and 2) the projection segment. When considering the transition between the two segments, we note that a potential bias could result from starting projections at a point on the tail end of the empirical distribution where the numbers at risk are relatively small and the Kaplan Meier estimates are associated with a high degree of uncertainty. To avoid this, parametric survival curves in the trial segment are fit to the data from time=0. The point at which the model transitions from trial to projection segment, is an input variable to the model and in the base case is set as described below. In the base case, the projection period ends at 30 years, approximating a lifetime.

Section 7.3.7 discusses the assumptions in the projection segment. The trial segment is detailed here as it relies on clinical data.

Dabrafenib and dacarbazine

Progression-free survival

PFS for dabrafenib and dacarbazine for the trial period are based on independent parametric survival distributions fit to individual patient data (IPD) from time zero on investigator-assessed PFS from the BREAK-3 trial (June 2012 data cut), the latest data cut for this endpoint) using AFT regression (SAS PROC LIFEREG). Investigator-assessed PFS is more likely to reflect progression as assessed in typical clinical practice than blinded independent central review (BICR) assessed PFS.

Independent survival distributions were estimated for dabrafenib and dacarbazine (i.e. proportionality of hazards was not assumed). The trial periods for dabrafenib and dacarbazine were defined as 53.1 weeks for dacarbazine and 71.1 weeks for dabrafenib based on the last censor or observed failure time for investigator-assessed PFS in BREAK-3.

Curve-fitting followed standard methodology and exponential, Weibull, log-logistic, log-normal and Gamma distributions were considered. Goodness-of-fit statistics and AUC comparisons are reported in Appendix **Error! Reference source not found.**. The AUC for PFS for dabrafenib and dacarbazine to end of follow up were relatively insensitive to the choice of survival distribution. The differences between the Kaplan-Meier and fitted distributions were least for the three-parameter Gamma distribution. Not unexpectedly, the one parameter exponential model does not generally provide a good fit. Although the three-parameter gamma distribution generally provides a good fit, it tends to generate a long tailed distribution that may bias the comparison versus the active treatment. Amongst the other two-parameter models, the curves and fit statistics are very similar. However, the log-normal tends to provide the best fit (marginally) followed by the log-logistic. The log-normal distribution was therefore used to model PFS during the trial period (and projection period, see Section 7.3.7) for dabrafenib and dacarbazine.

Overall survival (OS)

OS for dabrafenib during the trial period was based on an independent parametric survival distribution fit to individual patient data from the BREAK-3 (Dec 2012 datacut) study using AFT regression. As for PFS, exponential, Weibull, log-logistic, log-normal and Gamma distributions were considered. The distributions were evaluated using goodness of fit statistics, by comparing the AUC for the fitted distributions to those for the empirical distributions, and by visual inspection (see appendix 10.17). The log-normal distribution was deemed to provide the best fit to the empirical data and was used to model dabrafenib OS during the trial period. The duration of the trial period for dabrafenib was defined as 96 weeks based on the maximum censor or failure time for dabrafenib OS in BREAK-3.

For dacarbazine, the RPSFT analysis (rather than the intent-to-treat [ITT] analysis) was used to account for the confounding effect of crossover on OS in the BREAK-3 trial (see Section 6.3.6). As a consequence of a relatively small number of randomised patients, the relatively short follow-up in BREAK-3, and the recensoring of observations in the RPSFT algorithm, data on RPSFT adjusted OS for dacarbazine is sparse. Given the small amount of empirical data available for dacarbazine and the resulting uncertainty associated with fitting parametric curves to these data, OS for dacarbazine was modelled as proportional hazards versus dabrafenib (using the RPSFT adjusted HR from BREAK-3). See below for a discussion of this assumption. This HR was applied during the trial period for dabrafenib (i.e. 96 weeks), after which it was assumed there was no further effect of treatment.

Vemurafenib

In the base case, vemurafenib was modelled as proportional hazards versus dabrafenib, utilising the HRs for PFS and OS from the indirect treatment comparison of dabrafenib versus vemurafenib. The estimated PFS HR was applied throughout the entire model timeframe. For OS, the HR was applied during the trial period for dabrafenib monotherapy (i.e. 96 weeks), after which no further effect of treatment was assumed. Table 49 below summarises the clinical data used in the economic model during the trial period of modelling.

Proportional hazards assumption

As described above parametric distributions for both PFS and OS were fitted to the dabrafenib Kaplan-Meier data from the BREAK-3 trial. An independent parametric distribution was fitted to the dacarbazine Kaplan-Meier data from BREAK-3 for PFS. For dacarbazine OS, we assumed dacarbazine had proportional hazards to dabrafenib during the trial period and applied the RPSFT adjusted HR from BREAK-3. For vemurafenib we assumed proportionality of hazards during the trial period in order to apply the HRs obtained from the indirect treatment comparisons (see Section 6.7).

The comparison of average HRs over the same period is more or less appropriate as long as the underlying hazards are not changing substantially within that period. Data were available on the patients in the control arm of BREAK-3 out to 14 months (follow-up periods reported here will be shorter than those reported for the ITT analyses due to re-censoring in the control arm which is a feature of the RPSFT analysis) therefore the potential for bias in the analysis due to non-proportionality must be recognised. Figure 12 below plot the HRs (on the log scale) for OS

(RPSFT-adjusted) from the dabrafenib and vemurafenib trials obtained from the Kaplan Meier curves (on the basis of quarterly assessments).

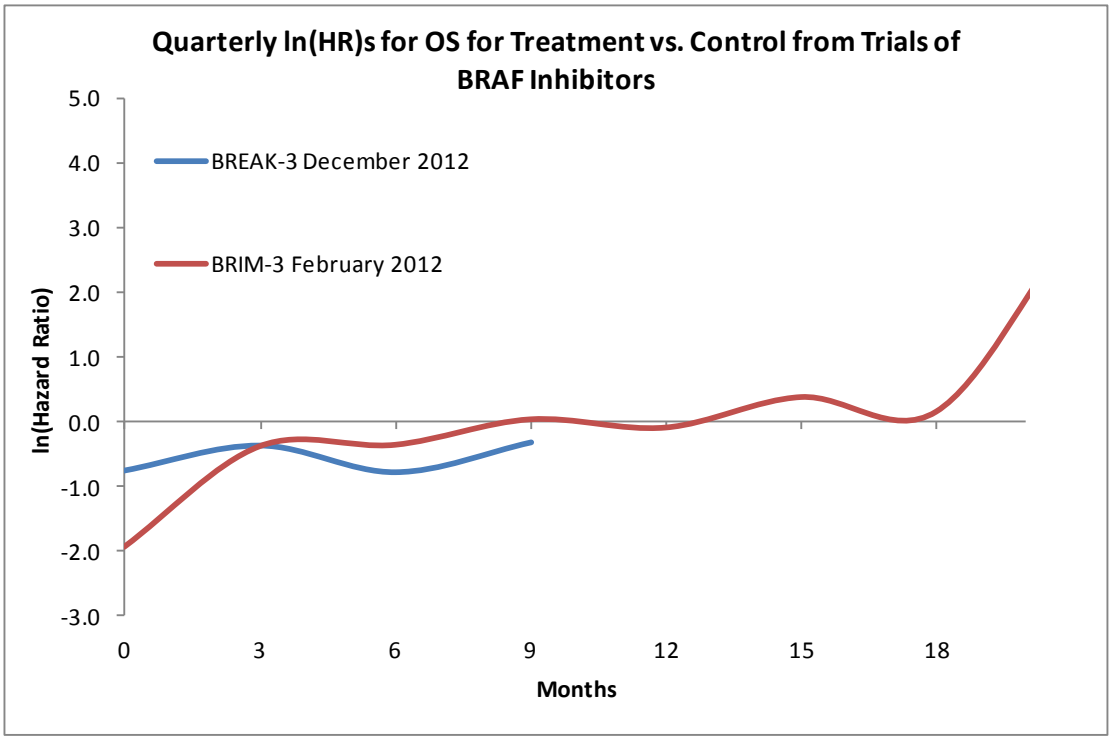


Figure 12. Quarterly ln(HR)s for OS for treatment vs control from trials of BRAF inhibitors

There is no compelling evidence to suggest the HRs were increasing in BREAK-3 and therefore that HRs over longer periods of follow up would be greater than the observed HRs, in part justifying an assumption of proportional hazards for dabrafenib and dacarbazine.

For the indirect comparison with vemurafenib, the possibility that differences in follow-up for BREAK-3 and BRIM-3 affect the ITC of HRs must be acknowledged. There are other measures of treatment effect (besides the HR) that might have been used to conduct the ITC. For example, it is possible to conduct an ITC on the acceleration factors (AFs) from the RPSFTM analyses and apply the resulting values to the curves for dabrafenib or the combination, although this method is far less common and we have seen no example of it in a technology appraisal. Another alternative would have been to use the approach described by Ouwens and colleagues (2010)* for conducting a network meta-analysis of parametric survival distributions. This approach may address the limitations of conducting the analysis based on HRs only. There is little to suggest that an alternative approach would be associated with more accurate estimates and in this appraisal a more typical approach to synthesis of time-to-event outcomes, i.e. using an adjusted ITC of HRs was used to make the required comparison.

* http://onlinelibrary.wiley.com/doi/10.1002/jrsm.25/pdf

Table 49. Summary of PFS and OS evidence used in modelling (direct and indirect comparisons)

	Dabrafenib (BREAK-3) vs.			Dacarbazine vs.			Vemurafenib (BRIM-3) vs.		
	HR	95% CI		HR	95% CI		HR	95% CI	
PFS									
Dabrafenib	1.00	---	---	2.70	1.72	4.35	1.03	0.62	1.69
Dacarbazine	0.37	0.23	0.58	1.00	---	---	0.38	0.32	0.46
Vemurafenib	0.97	0.59	1.60	2.63	2.17	3.13	1.00	---	---
OS									
Dabrafenib	1.00	---	---	1.82	0.70	4.76	1.16	0.44	3.10
Dacarbazine	0.55	0.21	1.43	1.00	---	---	0.64	0.53	0.78
Vemurafenib	0.86	0.32	2.29	1.56	1.28	1.89	1.00	---	---

Shaded cells represent direct evidence; unshaded cells relate to ITCs; OS was adjusted for confounding due to treatment switching

7.3.2 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.

N/A – The proportions of patients in each treatment group that reside in each health state over time are derived from the PFS and OS survival functions. An area under the curve analysis is used to estimate mean time pre-progression and mean survival. The difference between the two curves provides an estimate of the mean time alive following disease progression.

7.3.3 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.

N/A.

7.3.4 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?

The model does not explicitly link intermediate to final outcomes, e.g. PFS:OS.

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

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**

[*] 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.

- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

We consulted two clinical experts in the field of metastatic melanoma and a health economist in the development of the economic model. The experts participated in an Advisory Board meeting and questionnaires, individual interviews or Delphi techniques were not employed. It was not necessary for experts to estimate any clinical parameters and variables given that the starting point for the model was the trial data. However, participants in the meeting were asked to comment on the validity of the approach to modelling during the trial and projection periods and about how well known and acceptable the methods to adjust for crossover were.

Additional questions were asked about methodology behind estimates of utility, face validity of the estimates that were incorporated (Section 7.4.10) and the appropriateness of assumptions and costs relating to adverse events and to other health state costs during the model lifetime (Section 7.5.4).

Summary of selected values

7.3.6 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 50 below summarises the effectiveness inputs into the economic model. A summary of cost and utility variables is provided in Table 62.

Table 50. Summary of effectiveness variables applied in the economic model

	Variable	Dabrafenib	Dacarbazine	Vemurafenib	
	EFFECTIVENESS				
Progression-free survival	Mu	3.747 (log-normal)	2.518 (log normal)	**As with dabrafenib**	**Section 7.3.1 and Section 7.3.7**
	Sigma	0.843 (log-normal)	0.981 (log normal)	**As with dabrafenib**	
	Proportional HR vs. dabrafenib	N/A	N/A	1.03 (0.62-1.69)	
Overall survival	***Trial period***				
	Mu	4.456 (log-normal)	N/A	**As with dabrafenib**	**Section 7.3.1 and Section 7.3.7**
	Sigma	1.006 (log-normal)	N/A	**As with dabrafenib**	
	Proportional HR vs. dabrafenib	N/A	1.82 (0.70-4.76)	1.16 (0.44-3.10)	
	Projection period – AJCC				
	Parameter 1	0.024 (log-logistic)	**As with dabrafenib**		
	Parameter 2	1.015 (log-logistic)	**As with dabrafenib**		**Section 7.3.7**
	OS post 10 years : General population death rates are based on the proportion of men/women in BREAK-3 and the mean age of patients in the trial plus 10 years.				

7.3.7 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.

Costs and clinical outcomes are extrapolated beyond the end of the trial period out to 30 years (approximating a lifetime).

Projection of progression-free survival

For dabrafenib and dacarbazine, parametric survival distributions that had been fitted to patient level data from time zero were extrapolated beyond the end of trial follow-up. The curve fitting methodology, selection and outputs are described fully in Section 7.3.1. PFS data from the trials were mature and this approach was considered appropriate to approximate outcomes beyond the study period for this endpoint. Comparable to the approach taken during the trial period of the model (Section 7.3.1), PFS for vemurafenib was modelled as proportional hazards versus dabrafenib during the projection period too. The estimated hazards were applied throughout the entire model timeframe. PFS estimates for dabrafenib, dacarbazine and vemurafenib used in the model are shown in Figure 13.

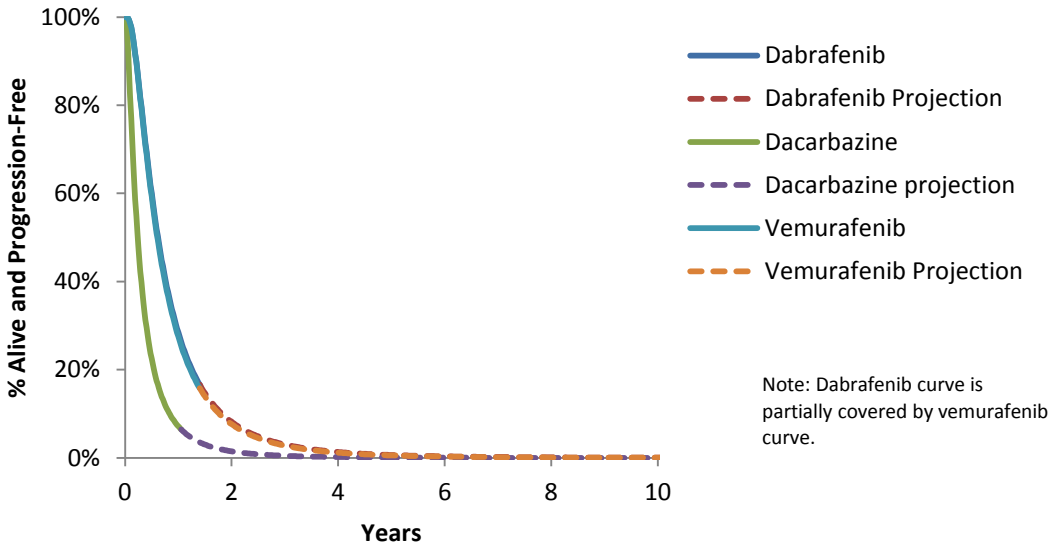


Figure 13. PFS extrapolations for dabrafenib, dacarbazine and vemurafenib in the economic model

Projection of overall survival

As described previously (Section 7.3.1), a log-normal distribution was fitted to the empirical OS data for dabrafenib during the trial period of the model.

In light of the uncertainty associated with overall survival projections of OS beyond the end of follow-up, it may be appropriate to supplement OS data from the BREAK-3 trial with OS data from secondary sources. As summarised in Appendix **Error! Reference source not found.**, RPSFTM-adjusted OS data for vemurafenib from BRIM-3 were combined with OS for dacarbazine from the ipilimumab plus dacarbazine Phase III trial, as well as data from the Surveillance Epidemiology and End Results (SEER) database in the vemurafenib NICE submission to obtain long term projections of OS for dacarbazine (long term mortality was also constrained to be less than general population mortality from life table data). This general approach of combining trial data with data from secondary sources to project OS was accepted by the NICE Appraisal Committee as appropriate. A similar approach was taken in this evaluation:

OS for dabrafenib during the projection period (from end of trial follow-up) out to 10 years was based on OS data from the AJCC registry.[19] Balch et al, 2009 provide survival data out to 10 years for 7,635 patients with metastatic melanoma by site of their metastases (skin, subcutaneous, or distant nodes; lung with or without skin/subcutaneous; and nonpulmonary visceral). These survival curves were digitized and then combined by weighting the curves based on the relative proportions of patients in the BREAK-3 study in the corresponding stages (16% M0/M1a [no metastases/distant skin, subcutaneous, or nodal metastases LDH normal], 18.4% M1b [metastases to lung], 65.6% M1c [metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH]).[7,104]

As shown in Figure 14, a log-logistic distribution provided an excellent fit to the AJCC OS data and was used in the model to reduce the number of parameter estimates required.

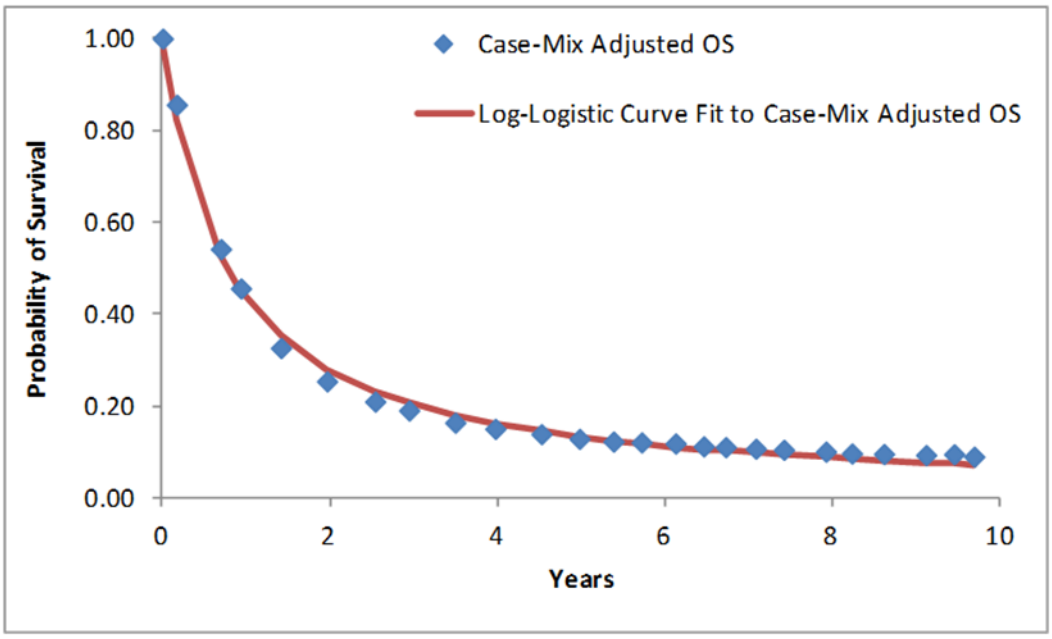


Figure 14. BREAK-3 case-mix adjusted OS from AJCC melanoma registry: Kaplan-Meier estimates and log logistic fitted curve

Based on the AJCC logistic distribution, OS at 24 months (the end of the trial period) was 29%. This compares with OS of 24% based on the lognormal survival curve for dacarbazine used for the trial segment of the model, and represents a reasonably high degree of concordance of the two sources.

Beyond 10 years (the duration of follow-up in the AJCC melanoma registry data), survival was based on UK general population mortality data.[105]

In this piecewise approach to modelling, it is assumed that there is no additional treatment effect of dabrafenib beyond the last observed event or censor time for OS in the BREAK-3 trial.

Similarly to the approach taken during the trial period of the model (Section 7.3.1), OS for dacarbazine and vemurafenib were modelled as proportional hazards versus OS for dabrafenib during the projection period. The estimated hazards were applied throughout the entire model timeframe.

OS projections for dabrafenib, dacarbazine and vemurafenib used in the model are shown in Figure 15 below.

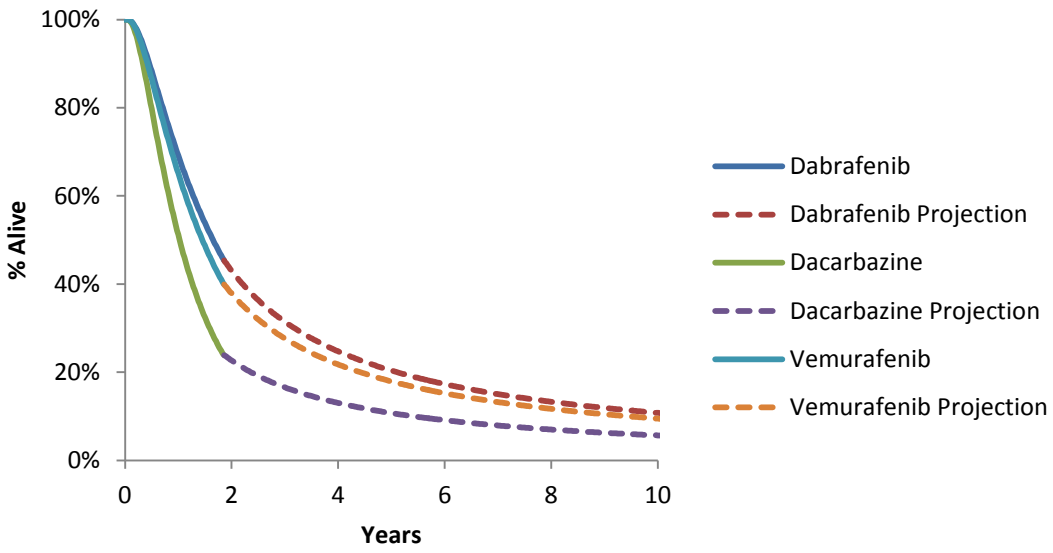


Figure 15. OS estimates for dabrafenib, dacarbazine and vemurafenib used in the model

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

Assumption	Justification
Treatment duration for dabrafenib represents exposure data in the BREAK-3 clinical trial	This means there is no requirement to make assumptions about duration of treatment and progression
The pre-progression and post-progression utility values for dabrafenib and dacarbazine were based on weighted averages of utility assessments (excluding baseline) among patients in BREAK-3.	Data directly from a randomised trial of targeted agents was considered more robust than relying on literature and is consistent with the NICE reference case.
Utility values for vemurafenib were assumed to be the same as those for dabrafenib.	Utility data for vemurafenib were not available.
In the absence of head-to-head data, vemurafenib is implemented in the model using the results of the indirect treatment comparison of dabrafenib versus vemurafenib, assuming proportional hazards to dabrafenib.	In the absence of head to head data, results from the indirect treatment comparison were considered to be the most robust estimate of relative efficacy. However, a sensitivity analysis where a class effect for dabrafenib and vemurafenib is assumed is also provided.
OS for dacarbazine is implemented in the model using the RPSFT adjusted HR from BREAK-3, assuming proportional hazards to dabrafenib.	Confounding due to cross-over in BREAK-3 and the resulting RPSFT adjustment means that there is limited dacarbazine data on which to fit parametric curves, although this would have been possible. A more robust approach was felt to be the assumption of proportional hazards to the dabrafenib OS data. A sensitivity analysis utilising the RPSFT adjusted Kaplan-Meier data for the trial segment of the model is provided.
30 years approximates a lifetime horizon	The mean age of patients in the model is 53 years and a 30-year horizon was considered adequate to represent the patient lifetime.
In the class effect analysis, PFS and OS for vemurafenib is represented by dabrafenib data, while adverse events are those reported in the BRIM-3 study of vemurafenib versus dacarbazine	This approach is considered more reasonable than the alternative approach where dabrafenib is represented by vemurafenib PFS and OS (in which case the dabrafenib data from the BREAK-3 trial is ignored); this approach is explored through sensitivity analysis. Adverse event data for vemurafenib is taken from BRIM-3 as there are notable differences in dabrafenib and vemurafenib's advere event profiles.
There are no costs associated with administering oral medications (dispensing costs are included)	It is a reasonable assumption that once dispensed, there are no further costs associated with administering oral therapies; dabrafenib and vemurafenib are likely to be prescribed every 28 days and patients will self-administer treatment .

Administration costs for dacarbazine (IV therapy) include the cost of dispensing the drugs	Administration of dacarbazine is costed using 2011/2012 NHS Reference Costs for delivery of simple parenteral chemotherapy at a first attendance (SB12Z Deliver Parenteral Chemotherapy at first attendance) once every 21 days (3 week cycle); we assume that this unbundled chemotherapy delivery HRG code includes pharmacy costs
A 28-day supply of dabrafenib or vemurafenib is dispensed every 28 days	This assumption was validated with clinical experts during an advisory board and the assumption is consistent with that made in the vemurafenib appraisal.
No wastage is assumed for dacarbazine	Dacarbazine is available in multiple formulations as a powder for reconstitution, so it is assumed to be straightforward to deliver the required dose without any wastage
The model assumes that dabrafenib and vemurafenib are dispensed every 28-days and that the entire cost of the therapy is incurred at the start of the 'cycle'; implicit in this is the assumption that any unused medication would be discarded if the patient discontinues treatment partway through a 28-day 'cycle'	This assumption is likely to reflect real life use of these medicines, i.e. that a patient's prescription is not used by another patient following discontinuation
By implementing relative dose intensities, the model assumes that patients with treatment interruptions retain and use unused medication from prior cycles in subsequent ones	Again, this assumption is likely to reflect real life use of these medicines (which are dispensed in 7-day packs), i.e. that patients will not discard their medication if they down dose during a 28-day period

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Melanoma can significantly impact on Health Related Quality of Life (HRQoL) throughout its stages and several studies have attempted to quantify this.[25,106,107] Up to one third of melanoma patients experience considerable levels of distress, mostly at the time of diagnosis and following treatment.[25] It is reasonable to expect that this will be considerable in patients with metastatic disease, where performance status is considerably poorer and deteriorates faster in comparison to earlier stages.[108] The systematic review of HRQoL conducted for this appraisal suggested that patients with metastatic melanoma had very poor HRQoL in the immediate time period following diagnosis, during the treatment period and following disease progression. Further to this, disease appeared to have a considerable negative impact on physical and emotional activities, levels of tiredness and mood.

During treatment, poor quality of life scores can be linked to the adverse events associated with therapy.[109,110] As the treatment for melanoma becomes more aggressive, significantly poorer mental and physical functioning is seen in melanoma patients.[25] However, HRQoL has been reported to gradually increase in the long term.[25,111] In a study of patients with metastatic melanoma, Overall State of Health (OSH) and General Health Perception (GHP) scores decreased right after treatment initiation and then gradually increased over the study period.[111]

Anxiety is common in the post-treatment follow-up stage[112] and patients may have considerable psychological needs[113,114] relating to fear of cancer progression,[25,113,115,116] uncertainty about the future and lack of information. [113,117] One study found that 73% of moderate- to high-risk patients reported levels of fear of cancer recurrence indicative of a need for some intervention.[118] One study found that cancer-related distress among long term melanoma survivors was more likely to be associated with female gender and younger age (20-49 years).[77,119]

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

On the basis of their systematic review of the literature addressing quality of life in patients with malignant melanoma, Cornish et al, 2009[25] propose that there are three distinct periods which impact upon HRQoL during the melanoma experience: diagnosis, treatment and follow-up.

During treatment, HRQoL is likely to be impacted by clinical response states, particularly whether a patient is experiencing partial response, stable disease or progressive disease. In addition utility decrements are associated with different toxicities.[98] Patients with advanced disease and those treated with aggressive regimens may therefore be the most likely groups to experience a significant impact on their HRQoL.

HRQoL data derived from clinical trials

7.4.3 If HRQoL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQoL 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.**

As described in Section 6.3.5, BREAK-3 assessed HRQoL using the EuroQol 5D (EQ-5D) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30).[48,77]

Evaluation of HRQoL through EQ-5D directly from patients using the validated, generic, choice-based EQ-5D is consistent with the NICE reference case.[65]

Mapping

7.4.4 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.**

It was not necessary to map utilities or quality of life data from the clinical trials. Utility data used in the economic model were derived directly from the BREAK-3 trial.

HRQoL studies

7.4.5 Please provide a systematic search of HRQoL 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 10.12, appendix 12.

An independent systematic review was conducted to identify relevant HRQoL data. The databases were searched for HRQoL and utility studies alongside the search

for economic studies (details of the search strategies are provided in Appendix 1**Error! Reference source not found.**.18).

7.4.6 Provide details of the studies in which HRQoL 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.**

A total of 36 HRQoL studies were identified by the systematic review (initial search in April 2012). All of the studies recruited adult patients with metastatic melanoma, an ECOG/WHO performance status of 0 to 2 and presented data for patients with stage III and/or stage IV disease. A broad range of tools was used to assess HRQoL across the studies. Overall, HRQoL scales revealed that patients with metastatic melanoma had very poor HRQoL in the immediate time period following diagnosis, during the treatment period and following disease progression. Further to this, disease appeared to have a considerable negative impact on physical and emotional activities, levels of tiredness and mood. It was not necessary for the cost-effectiveness model to map utilities from HRQoL data in these studies and only those studies reporting utility data directly are reported in this discussion. The full systematic review is available upon request from the manufacturer (118 pages).

Utility data were reported in five studies identified by the original systematic review; an update search and screen for additional studies published to 24 October 2013 found no additional utility studies of relevance. Two studies (USA) reported utility data in patients with stage III and stage IV melanoma [24,120]. The first study aimed to develop a reliable mapping function to impute EQ-5D health utility values from

Functional Assessment of Cancer Therapy-Melanoma (FACT-M) quality of life scores collected from a prospective study of melanoma-related HRQoL to validate FACT-M at a tertiary cancer care centre in Texas.[120] The study itself was presented in another publication, and was not separately eligible for discussion here as it did not discuss the EQ-5D results directly.[121] Askew et al 2011 report the EuroHRQoL-5D (EQ-5D) utility scores from this study, noting that they did not differ significantly between patients with stage III and stage IV melanoma (0.85 *vs.* 0.86 respectively).[120]

The second US study, King et al.,[24] established the impact of stage III and stage IV melanoma by comparing utilities across different stages of melanoma and time from initial diagnosis. Utilities were measured in consenting adult patients with melanoma using the time trade-off method. The 1997 American Joint Committee on Cancer criteria was used to stage the disease and divided cases into new and established groups (1 year or less after diagnosis and more than 1 year after diagnosis respectively) for stage I-III patients. Established stage IV melanoma was defined as more than 6 months after diagnosis. The utilities for new and established cases of melanoma diagnosis for stage III and stage IV patients are summarised in Table 51. Unexpectedly, it was observed that the mean utility value was significantly higher (p=0.01) in patients with newly diagnosed stage IV melanoma in comparison to newly diagnosed stage III patients (0.693 vs. 0.534 respectively). However, this may be explained by the relatively small sample sizes (11 subjects and 8 subjects respectively). In contrast, the mean utility value was significantly lower (p=0.01) in patients with established stage IV melanoma in comparison to established stage III patients (0.908 vs. 0.527).

Table 51. Utilities for new and established melanoma diagnosis

Stage	New diagnosis Mean (SD)	Established diagnosis Mean (SD)
III	0.534 (0.291)	0.908 (0.123)
IV	0.693 (0.329)	0.527 (0.339)

The third study, reported in a conference abstract, was conducted in Canada and established utilities for advanced melanoma health states using a standard gamble technique in the general public [122]. The study reported that utility scores decreased with increasing severity of health states: partial response was the most valued health state (0.84) followed by stable disease (0.79), progressive disease (0.55) and finally best supportive care (0.54). One day out/inpatient care and hospitalisation for grade 3/4 toxicities were associated with disutilities of -0.11 and -0.15 respectively.

The fourth study compared different measures (standard gamble, EQ-5D and short form health survey [SF-36]) of health utilities in patients with advanced melanoma.[123,124] Data were available from a vignette-based standard gamble study in the general population for advanced melanoma. In addition, the pivotal trial for ipilimumab captured patient reported HRQoL data using the EORTC-QLQ-C30 and SF-36 generic health surveys (mapped to EQ-5D and SF-6D utility values respectively). Utility values from the RCT were compared with results generated from the vignette-based study. In the progression-free health state, standard gamble and EORTC data showed a high degree of correlation in utility values (0.77 *vs.* 0.80 respectively) although the SF-36 values were significantly lower (0.64). When comparing the post-progression to the pre-progression state, the standard gamble data showed a significant fall of 0.18 in expected utility. This is not mirrored in the patient data, with a fall of 0.04 and 0.02 in the EORTC and SF-36 data respectively.

The final utility study conducted in the UK and Australia employed standard gamble to establish societal preference values for advanced melanoma health states using a vignette approach in the general public [98]. Standardised health state descriptions were developed based on World Health Organisation response definition, common toxicity criteria, feedback from five clinical experts and three quality of life researchers. Four melanoma treatment-related response-based health states were subsequently identified: partial response, stable disease, progressive disease and best supportive care (to address patients who choose not to undergo treatment). Following standard gamble, all profiled health states were associated with decreased health preference values compared to full health, although partial response was ranked as the most preferred state, followed by stable disease, progressive disease and best supportive care. In general, Australians reported a lower impact of less severe health states, and a higher impact of more severe health states in comparison to the UK. Mean utility decrements (disutilities) for toxicity-related health states were also captured in the study, of which the greatest decrement was associated with two to five day hospitalisation for grade III/IV toxicity (Table 52 below).

Table 52. Utility values from vignettes study by Beusterien et al.[98]

	Australia		UK		All	
Health state	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
Clinical response states						
Partial response	0.91	0.01	0.85	0.02	0.88	0.01
Stable disease	0.83	0.01	0.77	0.02	0.8	0.01
Progressive disease	0.47	0.03	0.59	0.02	0.52	0.02
Best supportive care	0.46	0.03	0.59	0.02	0.52	0.02
Symptomatic melanoma	0.2	0.02	0.11	0.02	0.16	0.01
Utility decrement for toxicity states						
2–5-day hospitalisation for severe toxicity (grade III/IV)	0.20	0.02	0.13	0.02	0.17	0.01
1-day in-/outpatient stay for severe toxicity (grade III/IV)	0.14	0.01	0.11	0.02	0.13	0.01
Stomatitis (grade I/II)	0.14	0.01	0.10	0.02	0.13	0.01
Flu-like syndrome (grade I/II)	0.13	0.01	0.09	0.01	0.11	0.01
Nausea/vomiting (grade I/II)	0.12	0.01	0.07	0.01	0.10	0.01
Diarrhoea (grade I/II)	0.11	0.01	0.06	0.01	0.09	0.01
Skin reaction (grade I/II)	0.08	0.01	0.03	0.01	0.06	0.01
Hair loss (grade I/II)	0.03	0.01	0.03	0.01	0.03	0.01

Quality of life results are broadly consistent across the studies found. Askew et al (2011) noted utilities of 0.85 – 0.86 in patients with Stage III and IV melanoma which seems high given that these are comparable to UK population norms for the EQ-5D index in persons 45-54 years of age (the mean age of patients in the BREAK-3 trial was 53 years) from the York Measurement and Valuation of Health (MVH) study as reported by Kind and colleagues 1999.[125] Results from King et al are unexplained but the small number of patients with stage IV disease in the underlying study may cast doubt on the robustness of the findings. [24]

However, results from Hogg et al, 2010,[122] Beusterian et al, 2009[98] and the data from the ipilimumab trial that underpins the analysis in Batty et al, 2012[123,124] all provide

fairly consistent findings. The relationship between these results and those utilised in modelling are discussed below and the impact of varying utilities on cost-effectiveness is explored in the sensitivity analyses in the economic model, as described further in Section 7.6.

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

The most relevant study found in the literature review and utilised in previous appraisals of metastatic melanoma because it reports preferences in a UK population is Beusterian et al.[98] Results of this study are reported in Table 52 above. The utilities utilised in the economic model in this submission, which are derived from BREAK-3 and are described in Section 7.4.9 and are comparable to those from the Beusterian et al, 2009 study.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQoL.

Adverse events associated with therapy can impact on quality of life of patients receiving treatment for metastatic melanoma (see Section 7.4.1 and Section 7.4.2). Disutility associated with AEs was not taken into account as this was thought to be captured through the utility values for the pre and post-progression health states.

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

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Treatment group specific pre and post-progression utility values were estimated from BREAK-3 EQ-5D data. Pre-progression utility for each patient in BREAK-3 was calculated as the average of all pre-progression utility values. For each treatment group, the mean pre-progression utility was calculated as the average of all mean pre-progression utilities across all patents in the group with each patient weighted by the number of EQ-5D assessments that patient completed. The mean decrement in utility versus perfect health was calculated by subtracting the mean pre-progression utility from one.

The mean decrement in post-progression utility for dabrafenib was calculated as the average of the post-progression utility decrements of all patients within the group. The decrement in utility post-progression for dacarbazine patients was not calculated because any such estimate might be confounded due to crossover.
Table 53 displays the utility decrement values for dabrafenib and dacarbazine from BREAK-3 that were used in the model. Given that there is no clinical rationale for

assuming that HRQoL after progression differs by therapy, the decrement in utility for post- vs. pre-progression for dacarbazine was assumed to be the same as for dabrafenib.

Table 53: Utility Values

Decrement in Utility	Dabrafenib/Vemurafenib				Dacarbazine			
	N	Mean Decrement	SE	Actual utility value used	N	Mean Decrement	SE	Actual utility value used
Progression-free vs. perfect health	187	0.233	0.024	0.767	60	0.250	0.046	0.750
Post-progression vs. progression-free	37	0.090	0.056	0.677	*	0.073	*	0.677

*The decrement in utility post- vs. pre-progression for dacarbazine was not calculated because of potential confounding due to crossover and was assumed to be same as that for dabrafenib.
N = Total Number; SE = Standard Error

PPS utility for dabrafenib and dacarbazine are assumed to be the same at 0.677 (0.767-0.09); i.e. utility decrement upon progression for dacarbazine = 0.073 (0.750 - 0.677).

It should also be noted that the mean pre-progression utility values for dabrafenib from BREAK-3 (0.767) are somewhat lower than those used by Roche for vemurafenib and dacarbazine in their submission to NICE (0.806).[40] Also, the mean decrement in utility associated with progression among dabrafenib patients in BREAK-3 (0.090) is less than half that assumed by Roche in their NICE submission (0.806-0.590=0.216). Which of these two values better reflects the utility value of patients with melanoma after failure of first line therapy is uncertain. On the one hand, it is possible that the decrement in utility from BREAK-3 is an underestimate because the data were collected shortly after progression and therefore would not reflect any long-term decline in utility. On the other hand, the utility values from the vignette study that was the basis of the Roche estimates are highly dependent on the descriptions of the hypothetical health states. For this evaluation, we used the decrements in utility for progression that were estimated directly from BREAK-3, as this is more consistent with good practice guidelines for the assessment of utilities in economic evaluations.

Finally, lacking comparable EQ-5D utility data for vemurafenib, utility values for patients receiving vemurafenib were assumed to be the same as those for dabrafenib.

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

- **the criteria for selecting the experts**

[§§§] 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.

- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Experts attending the Advisory Board meeting described in Section 7.3.5 were asked for their opinion on the validity of the utility values applied in the economic modelling. Questions in this setting did not follow a formal methodology and as the utilities implemented in the model were derived from phase III trial data it was not necessary to estimate additional utility values during this forum. The advisors commented that the utility values used in the model had face validity and were not dissimilar to those utilised in previous appraisals of treatments in this disease area.

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

In the PFS health state, HRQoL is assumed to be dependent on response rates and adverse events. It is assumed that the utilities for dabrafenib and dacarbazine capture the impact of these characteristics as they are based on the underlying trial data. In the PPS health state for all therapies, HRQoL is independent of treatment or other factors. Estimates of the variance of utility values used for these health states were investigated through sensitivity analysis.

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

Utility decrements associated with AEs were not included in the model. The impact of adverse events was assumed to be captured by the utilities for dabrafenib and dacarbazine (as these were derived from the underlying phase III trial). Equivalent data for vemurafenib were not available. It was therefore assumed that vemurafenib was associated with the same utilities as dabrafenib.

7.4.13 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?

The model does not assume a baseline quality of life that is different to the health states.

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

HRQoL is impacted by total time in PFS and PPS health states, however within the states, HRQoL is assumed to be constant over time.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Modelled health states assume utilities as described in Section 7.4.9. The primary source of utility data is the BREAK-3 trial and values have not been amended for dabrafenib.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost-effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 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.

The principles of costing in the economic model were based on approaches taken in recent appraisals of vemurafenib and ipilimumab. Specifically, the model includes drug acquisition costs, dispensing and administration costs, AE costs and 'other' costs during progression-free and post-progression survival (which include costs of routine follow-up visits, lab tests and scans). One-off costs for diagnostic/screening cost, therapy initiation, progression and death are also included.

'Other' costs are in part derived from the submission to NICE for ipilimumab which in turn were derived from a survey of five UK clinicians conducted by Oxford Outcomes.[41] This microcosting approach is also consistent with that taken in the vemurafenib NICE appraisal.[40] Updated HRG codes and PSSRU information were applied and the face validity of the resulting costs was confirmed by UK melanoma consultants during an advisory meeting.

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

There are no HRG or PbR tariff codes specific to dabrafenib. NHS reference costs are relevant and appropriate when costing elements of care alongside drug treatments, including outpatient visits and radiological exams. These are detailed in the following sections.

Resource identification, measurement and valuation studies

7.5.3 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 10.13, 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.**

Seaches for resource use data were incorporated into the economic systematic review (details of the search strategies are provided in Appendix 1**Error! Reference source not found.**.15.

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

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Costs of health states in the model are as described in Section 7.5.6.

[****] 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.

In the absence of a comprehensive literature base, estimates of management costs for many of the adverse events included in the economic model were derived from clinical opinion [redacted]

Intervention and comparators' costs

7.5.5 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 7.2.2.

The economic model incorporates the following costs for each intervention and comparator:

- Acquisition of study medications
- Administration of study medications
- Monitoring of study medications
- Treatment of adverse events (AEs)
- Other costs during PFS
- Other costs during PPS

Table 54. Unit costs associated with dabrafenib in the economic model

Items	Dabrafenib	Ref. In submission
Technology cost	Dabrafenib (NHS list price): 28 day supply @ £5,600 (28x75mg: £1,400 | 28x50mg: £933.33) [redacted]	Section 1.10
Administration cost	N/A oral therapies	
Dispensing cost	£13.40 every 28 days	See Administration Costs below
BRAF testing	£206.34 / treated patient	See Administration Costs below

Table 55. Unit costs associated with the comparators in the economic model

Items	Vemurafenib	Dacarbazine	Reference in submission
Technology cost	Vemurafenib: (NHS list price): £1,750 per pack (56 tabs) = £7000/month [redacted]	1000mg/vial @ £31.80/vial = £0.03/mg = £82.00 /28 days* * Cost per 28 days provided for comparison. Dacarbazine is administered once every 21-day cycle. Cost per 28 days for dacarbazine calculated by multiplying 21-day cost (£61) by 28/21.	
Administration cost	N/A oral therapy	£203.16 NHS reference costs: SB12Z Deliver Parenteral Chemotherapy at first attendance	See Administration Costs below
Dispensing cost	£13.40 every 28 days	£0	See Administration Costs below
BRAF testing	£206.34 / treated patient	£0	See Administration Costs below

Cost of dabrafenib

The model assumes that a patient will be dispensed sufficient dabrafenib for 28 days of use once every 28 days. As a default, the model calculates the amount of medication and number of administrations of medication received based on the planned dose of the medication and the distribution of PFS, assuming patients are treated until progression. However, the actual amount of medication and number of administrations may differ from that based on these calculations due to dose

reductions, treatment interruptions, and differences between the distribution of time to discontinuation and the distribution of PFS. To scale for this, the model includes relative dose intensities (RDIs) for medication costs and for administration costs.

RDIs for medication costs and for administration costs were calculated for each study medication received in each arm of, BREAK-3 using individual patient data. The medication cost RDI for each medication was calculated as the ratio of the estimated actual cumulative dose to the estimated planned cumulative dose. The administration cost RDI for each medication was calculated as the ratio of the estimated actual cumulative number of administrations to the estimated planned cumulative number of administrations.

Actual and planned cumulative doses were estimated using the Kaplan-Meier sample average (KMSA) method:

- The actual cumulative dose was calculated as the sum over all study days of the product of the probability of being alive and on therapy each day and the mean dose among patients who were alive and on therapy on each day. The planned cumulative dose was similarly calculated as the sum over all study days of the product of the probability of being alive and progression-free on each day and the planned dose on each day.

- The actual number of days on therapy was calculated as the sum over all study days of the product of the probability of being alive and on treatment each day and the proportion of patients who were alive and on treatment and had a non-zero dose on each day. The planned number of days on therapy was calculated as the sum over all study days of the proportion of patients alive and progression-free on each day. Investigator-assessed PFS was used in the calculation of RDIs.

Table 56. Estimated RDIs from BREAK-3

Trial	Treatment	RDI	
		Medication	Admin
BREAK-3	Dabrafenib	1.02	1.05
BREAK-3	Dacarbazine	0.95	0.96

In the absence of data with which to calculate RDIs for vemurafenib in BRIM-3, it was assumed that the RDIs for vemurafenib would be the same as those for dabrafenib.

The use of RDI to adjust for treatment interruptions yields an estimate of the cost that is generally consistent with what would be obtained if usage was modelled explicitly, assuming that patients who experience treatment interruptions or down dosing will retain and use their unused medication from prior cycles in subsequent ones and that patients who discontinue in the middle of a cycle (e.g. due to progression or adverse events) would discard/waste unused medication after the last cycle.

Administration costs

Administration costs for dabrafenib are assumed to be immaterial because they are oral therapies. A dispensing cost for these oral medications was estimated by accounting for the time required by a hospital pharmacist to dispense the medicines. It was assumed that dispensing would require 12 minutes of time, the average required to dispense capecitabine in metastatic colorectal cancer.[126] PSSRU 2012 estimates that it costs £67 per hour for a hospital pharmacist to perform patient-

related activities (accounting for overheads, qualifications and salary on-costs). The base case therefore assumes that the cost of dispensing dabrafenib every 28 days was £13.40 (£67/(60/12)). This is the same approach followed in the vemurafenib NICE submission.[40]

Health-state costs

7.5.6 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 7.2.4.

Monthly state-specific costs of melanoma treatment during PFS and PPS were assumed as well as one-off costs for initiation of therapy and death.

Monthly costs by state were estimated by combining monthly resource use estimates from the NICE appraisal of ipilimumab with unit costs estimates from published sources. Medical resource use in the ipilimumab assessment was based on estimates from a survey of five UK clinicians regarding treatment of individuals in the UK diagnosed with stage III or stage IV melanoma who received active treatment with systemic therapy, outside of a clinical trial, or who received any form of supportive care.[41]

Other costs per month for each therapy were calculated as the sum of the product of estimated monthly utilisation of each service as described in detail in **Error! Reference source not found.** in Appendix **Error! Reference source not found.**. Included costs are summarised in Table 57 below and are assumed to be the same for all therapies.

Table 57. Health states and associated monthly costs in the economic model (costs are rounded for simplicity)

Health State	Service	Cost, £	Reference
PFS	Outpatient visit (GP and plastic surgeon)	5	NHS Ref Costs 2011-2012 (resource use from NICE ipilimumab submission)[41]
	Inpatient stay	15	
	Laboratory tests	7	
	Radiological exams	100	
	Total	**127**	
PPS	Outpatient visit (largely medical oncologist)	211	NHS Ref Costs 2011-2012 (resource use from NICE ipilimumab submission)[41]
	Inpatient stay	15	
	Laboratory tests	7	
	Radiological exams	100	
	Total	**333**	

One-time costs were also included for all patients receiving active treatment (as described in

Table 58).

Table 58. One-off costs associated with treatment in the economic model

Other cost	Value, £	Reference
Treatment initiation (one-time)	£337	Ipilimumab submission to NICE[41]
Death	£6,177	King's Fund, 2008[127]

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. 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 7.2.2.

The treatment-related adverse events considered in the model are those grade 3+ events with an incidence of 5% or greater for dabrafenib, vemurafenib or dacarbazine in either BREAK-3 or BRIM-3 and/or those that were considered important from a clinical or economic perspective based on the opinion of physicians participating in a GSK advisory board meeting. Other grade 1-2 events were not considered because they are generally self-limiting and are not therefore likely to be associated with substantial costs.

Estimates of the incidence of each AE by treatment are provided in Table 59. Estimates of incidence were obtained from BREAK-3 for dabrafenib and dacarbazine and from BRIM-3 for vemurafenib.

Table 59: Incidence of Treatment-related SAE (grade 3/4)

Adverse Event	Number of Patients Experienced Event		
	Dabrafenib (N=187)	Dacarbazine (N=59)	Vemurafenib* (N=336)
PPE	4 (2.1%)	0	--
Photosensitivity	0	0	40 (11.9%)
Pyrexia	6 (3.2%)	0	--
SCC	11 (5.8%)	--	40 (11.9%)
Neutropenia	0	8 (13.6%)	1 (0.3%)
Rash	0	--	28 (8.3%)
Keratoacanthoma	0	--	20 (5.9%)
-- Incidence not reported and is assumed to be 0.			

Notes: PPE: Palmar-plantar erythrodysesthesia; SCC: Squamous cell carcinoma
*Chapman et al. reports grade 2+ adverse events with >5% incidence in either treatment arm. Only grade 3+ incidence is reported in the table above, with the exception of photosensitivity, which is grade 2+

The cost of AEs included in the model are summarised in

Table 60.

Table 60. Summary of mean (SE) cost per AE used in the model (costs are rounded for simplicity)

Adverse Event*	Cost per Event, £	
	Mean	SE
Grade 3+		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Grade 1 or 2		
[redacted]	[redacted]	[redacted]

The cost of treating each AE is calculated by multiplying the incidence of the AE by the expected cost of the event. Estimates of the costs of treating neutropenia, rash, and SCC were based on the cost-of-illness study (see Section 7.5.3). Where costs were not directly available from this study, the following assumptions were made:

- Grade 3 or higher keretocanthoma was assumed to have the same cost as Grade 3 or higher SCC.
- Grade 3 or higher PPE was assumed to have the same cost as Grade 3 or higher rash.
- Pyrexia costs were assumed to include an outpatient visit to a medical oncologist (Currency Code 370-Consultant Led: Follow-up Attendance Non-Admitted Face to Face, NHS Ref Costs 2011-2012, NHS Trusts and NHS Foundation Trusts, £124) and a hospitalisation (£1,207, see appendix 10.21).

Miscellaneous costs

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

Costs of post-study anti-cancer therapy (PSACT) are also incorporated in the model into the PPS health state to account for any imbalances between the drugs being compared.

In BREAK-3, patients randomised to dacarbazine were more likely to receive PSACT than patients randomised to dabrafenib. For each treatment group in BREAK-3, the expected costs of PSACT per patient were calculated by summing the product of the proportion of patients receiving various PSACTs and the corresponding estimates of the cost of a single course of each therapy. The utilisation of PSACT in BREAK-3 and the characteristics and costs of the individual regimens are reported in further detail in Appendix **Error! Reference source not found.**.

The expected costs of PSACT per patient using this methodology are reported in Table 61. Lacking data on the utilisation of PSACT among patients receiving vemurafenib in BRIM-3, the costs of PSACT for vemurafenib were assumed to be the same as those for dabrafenib.

Table 61. Expected PSACT costs used in CE model

Comparators	Expected Cost	SE
Dabrafenib	£3,013	£2,461
Vemurafenib	£3,013	£2,461
Dacarbazine	£6,044	£3,283

The validity of the approach outlined above to incorporating PSACT costs into the model was explored with experts during an advisory board meeting. They commented that it would be appropriate not to include any PSACT costs given that in UK practice there is unlikely to be any relationship between the type of PSACT (and therefore the cost) and the first line treatment that was received. Metastatic melanoma patients who progress following their first line treatment will go on to receive four doses of ipilimumab. An approach where PSACT costs are assumed to be zero is therefore incorporated into deterministic sensitivity analyses.

Personal and social service costs have not been considered; they are not expected to be significant and are assumed to be similar for all comparators.

Table 62. Summary of cost and utility variables applied in the model

	Dabrafenib monotherapy		Vemurafenib		Dacarbazine		
Variable	**Value**	**SE**	**Value**	**SE**	**Value**	**SE**	**Reference to section in submission**
COSTS							
Drug utilisation							
Mg per day of use	150mg BID		960mg BID				
RDI – medication	1.02		1.02		0.95		Section 7.5.5
RDI – administration	1.05		1.05		0.96		
Unit costs							
Cost per unit	Dabrafenib – LIST PRICE 28x75mg = £1,400 [redacted]		[redacted]				Section 7.5.5
Administration/28 days	£13.40		£13.40		£203.16		
Other PFS costs/month	£127	£32	£127	£32	£127	£32	
Other PPS costs/month	£333	£83	£333	£83	£333	£83	
PSACT	£3,013	£2,461	£3,013	£2,461	£6,044	£3,283	
One-off costs							Section 7.5.5
Therapy initiation	£337	£84	£337	£84	£337	£84	
BRAF testing	£206.34/treated patient	£52	£206.34/treated patient	£52	testing not applicable		

Death	£6,177	£1,544	£6,177	£1,544	£6,177	£1,544	
Patient starting age in the model	53						Section 6.3.4
% male in the model	59.60%						BREAK-3 patient level data
Mean body surface area	1.93 (SE 0.22)						
Mean body weight	80.13kg (SE 18.00)						
Utility values							
Progression-free decrement versus perfect health	0.233	0.024	0.205	0.046	0.233	0.024	Section 7.4.9
Post-progression decrement versus progression free	0.09	0.056	0.073	*	0.090	0.056	

*The decrement in utility post- vs. pre-progression for dacarbazine was not calculated because of potential confounding due to crossover and was assumed to be same as that for dabrafenib.

7.6 Sensitivity analysis

7.6.1 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.

Section 7.3 describes how clinical data were implemented into the model and how clinical outcomes were extrapolated beyond trial follow-up periods. Structural uncertainty has been investigated by fitting alternative survival functions for PFS and for OS and by exploring the impact of not adjusting for crossover. The impact of assuming a 10 year time horizon is also assessed (see section 7.6.2).

7.6.2 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 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Table 63 details the scenarios investigated in deterministic sensitivity analyses along with the rationale for each set of changes.

Table 63. Deterministic sensitivity analysis scenarios

1	Time horizon set to 10 years	Horizon is a potential sensitivity in the economic model, particularly given the accrual of benefit post progression
2	BRAF class effect	Explores the impact of a class effect assumption for dabrafenib and vemurafenib. This analysis assumes that vemurafenib has exactly the same PFS and OS as dabrafenib
3	PFS for dabrafenib and dacarbazine – Weibull	Explores the impact of the use of different parametric curve fitting for dabrafenib and dacarbazine PFS.
4	PFS for dabrafenib and dacarbazine – gamma	
5	PFS for dabrafenib and dacarbazine KM data	Utilises the empirical Kaplan-Meier data for the PFS trial segment for dacarbazine and dabrafenib. PFS projection segment based on log-normal distribution fitted to idependent Kaplan-Meier data for dabrafenib and dacarbazine
6	OS for dabrafenib – Weibull	Explores the impact of the use of different parametric curve s for dabrafenib OS during the trial segment.
7	OS for dabrafenib - log-logistic	
8	OS for dabrafenib – gamma	

9	OS for dabrafenib based on Kaplan-Meier data	Utilises dabrafenib Kaplan-Meier data for the OS trial segment
10	OS for dacarbazine (trial segment) based on RPSFT-adjusted Kaplan-Meier data	The base case derives a survival curve for dacarbazine by assuming proportional hazards to dabrafenib. This analysis utilises the RPSFT-adjusted Kaplan-Meier data for the PFS trial segment for dacarbazine
11	OS for dacarbazine (trial segment) based on proportional hazards versus dabrefnib using ITT HR from BREAK-3	The base case applies the HR from the RPSFT adjusted analysis of BREAK-3 to the survival data for dabrafenib to obtain a survival curve for dacarbazine for the OS trial segment. This analysis uses the unadjusted ITT HR from BREAK-3.
12	Survival for dacarbazine based on AJCC survival for entire model timeframe, dabrafenib and vemurafenib based on proportional hazards vs. dacarbazine	OS data for the dacarbazine arm is confounded by cross over. Registry data (e.g. AJCC) may provide the best estimate of survival prior to the introduction of BRAF inhibitors.
13	Survival for dacarbazine and vemurafenib based on approach taken for vemurafenib NICE submission, dabrafenib based on proportional hazards vs. vemurafenib	Digitisation software was used to create pseudo individual patient data from the survival curves reported in the vemurafenib manufacturer submission to NICE. This analysis explores the impact of using the BRIM-3 data for vemurafenib and dacarbazine and applying a proportional hazards assumption for dabrafenib.
14	HR for PFS for dabrafenib vs. dacarbazine (lower CI)	Comparative efficacy is an important parameter in the model and the impact of assuming higher and lower limits of the HRs obtained through direct and indirect comparisons (which included adjustments for crossover) is assessed.
15	HR for PFS for dabrafenib vs. dacarbazine (upper CI)	
16	HR for PFS for dabrafenib vs. vemurafenib (lower CI)	

17	HR for PFS for dabrafenib vs. vemurafenib (upper CI)	
18	HR for OS for dabrafenib vs. dacarbazine (lower CI)	
19	HR for OS for dabrafenib vs. dacarbazine (upper CI)	
20	HR for OS for dabrafenib vs. vemurafenib (lower CI)	
21	HR for OS for dabrafenib vs. vemurafenib (upper CI)	
22	Perfect dose intensity for all comparators	Assesses the impact of assuming no dose interruptions which may reflect ideal clinical practice where adverse events are perfectly managed
23	Admin costs set to +50% of base case value	Costs of administration may vary across different locales and the impact of higher of lower administration costs are explored
24	Admin costs set to -50% of base case value	
25	PF costs set to +50% of base case value	Other costs in the PFS state depend upon treatment practice, i.e. relate to regular monitoring and follow-up for patients. These costs may vary in practice and across localities
26	PF costs set to -50% of base case value	

27	PP costs set to +50% of base case value	As above, other costs in the PPS health state (apart from PSACT costs) relate to a 'one off' progression cost which depends upon resource use assumptions. These costs may vary in practice
28	PP costs set to -50% of base case value	
29	Testing costs set to +50% of base case value	Diagnostic test costs in the model are based on the cost of the Cobas BRAFV600 mutation test; these analyses explore the impact on cost-effectiveness of using a more or less expensive test
30	Testing costs set to -50% of base case value	
31	PSACT cost set to +50% of base case value	PSACT will be dependent on local treatment practice. A group of UK consultants suggested that PSACT not be included in the model as PSACT would not vary according to 1L treatment.
32	PSACT cost set to -50% of base case value	
33	PSACT cost set to zero	
34	Terminal care cost set to +50% of base case value	Explores the impact of varying end of life costs which may vary in practice.

35	Terminal care cost set to -50% of base case value	
36	Costs of all AEs simultaneously set to +50% of base case value	The model estimates the costs of treating AEs by multiplying expected incidences by the cost of treatment. These scenarios explore the impact of varying the cost of treating adverse events around the values used in the base case
37	Costs of all AEs simultaneously set to -50% of base case value	
38	Set cost of all adverse events to zero	
39	Disutility of PFS vs. perfect health set to -50% of the base case value	Utility values utilised in modelling are comparable although not exactly the same as values utilised in the vemurafenib appraisal. These scenarios explore the impact of varying utility value estimates for pre-progression health states to assess the impact of this potential sensitivity on cost-effectiveness.
40	Disutility of PFS vs. perfect health set to +50% of the base case value	
41	Disutility of PPS vs. PFS for dacarbazine assumed to be same as dabrafenib	This analysis assesses the impact of assuming one utility value for the PFS health state, set at the dabrafenib value.
42	Disutility of PPS vs. PFS set to -50% of the base case value	Utility values utilised in modelling are comparable although not exactly the same as values utilised in the vemurafenib appraisal. These scenarios explore the impact of varying utility value estimates for post-progression health states to assess the impact of this potential sensitivity on cost-effectiveness.

43	Disutility of PPS vs. PFS set to -50% of the base case value	

7.6.3 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 7.3.6, 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 undertaken by simultaneously sampling from the estimated probability distributions of the model parameters to obtain 1,000 sets of model input estimates. For each simulation, expected costs and QALYs were calculated for each comparator, along with the differences between comparators in expected costs and QALYs. Ninety-five percent CIs were calculated for expected costs and QALYs and the differences in expected costs and QALYs based on the 2.5 and 97.5 percentiles of these simulations. For each comparison, simulation results were plotted on the cost-effectiveness plane. Cost-effectiveness acceptability curves (CEACs) were constructed for pairwise comparisons of each intervention vs. the relevant comparators. Additionally, CEACs were constructed on an incremental basis in order to determine the proportion of simulations in which each comparator was cost-effective compared to others.

Further detail of parameter sampling is provided in Table 64 below.

Table 64. Parameter sampling in probabilistic sensitivity analyses

Parameter	Detail
Log-normal distributions for PFS and OS	PFS and OS were sampled from bootstrapped Kaplan-Meier survival distributions. Sampled distributions of PFS and OS were were derived using log-normal distributions fitted to the data from the corresponding bootstrap sample.
HRs for PFS and OS	Sampled assuming that the natural log of the HR follows a normal distribution
Decrements in utility for pre-progression from perfect health and for post-progression vs. pre-progression	Sampled independently assuming log-normal distributions (to ensure the utility value would not exceed 1.0)
Decrements in utility from pre-progression to post-progression for dabrafenib	Assumed to be such that post-progression utility always would be the same as that for dabrafenib
Probabilities of AEs	Sampled independently for each AE and comparator using beta distributions
Medication prices	Assumed to be known (not random variables) and were not sampled in the PSA
Other costs	Sampled assuming log-normal distributions with the SEs assumed to be 25% of the base case values

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), 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 65 below summarises the model results compared with clinical data for the dabrafenib and its comparators.

Table 65. Summary of model results compared with clinical data

	Dabrafenib monotherapy			*Vemurafenib*			*Dacarbazine*		
	Clinical trial result (months)	*Clinical trial result (weeks)*	*Model result (weeks)*	*Clinical trial result (months)*	*Clinical trial result (weeks)*	*Model result (weeks)*	*Clinical trial result (months)*	*Clinical trial result (weeks)*	*Model result (weeks)*
PFS (median)	6.9[5]	30	32	6.9[84]	30	32	1.6 [84] to 2.7 [5]	7 to 12	12
PPS (median; weeks) [OS-PFS]		49	51		29	43		31.6	42
OS (median)	18.2[5]	79	83	13.6 [84]	59	75	8.9 [BRIM-3 adjusted for Xover) [84]	39	54

For PFS there is consistency in the modelled and observed results.The consistency between modelled PFS results and PFS trial data is important because of the positive association between PFS and incremental medication costs, with the majority of costs accruing in the PFS health state. For dabrafenib, model predicted OS results are comparable to those reported in clinical trials. For dacarbazine and vemurafenib, model-predicted OS estimates are higher than those seen in clinical trials. This inconsistency in the model-predicted OS results, is due to the fact that OS is predicted on the basis of an underlying proportional hazards assumption to dabrafenib monotherapy. The better OS predicted by the model for dacarbazine and vemurafenib may over-estimate survival benefit, which in turn may overestimate the ICERs for dabrafenib. The estimates of cost-effectiveness for dabrafenib presented in this submission are therefore conservative.

7.7.2 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.

Not applicable.

7.7.3 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.

In the model QALYs are generated on the basis of the proportion of patients and the time spent in each health state (PFS, PSS). The proportion of patients over time in each state is estimated through curve fitting and extrapolation as described in detail in Section 7.3.

7.7.4 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.

Table 66 provides the disaggregated life years and QALYs accrued for each intervention.

Table 66. Expected LYG and QALYs by health state for all interventions

	Dabrafenib	Vemurafenib	Dacarbazine
LYG			
PFS	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
QALYS			
PFS	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

7.7.5 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.

Disaggregated incremental QALYs and costs by health state for each intervention (at PAS prices) are presented in the tables below. Disaggregated costs (at list price) are presented in Appendix **Error! Reference source not found.**.

Table 67. Incremental QALYs by health state

		Versus vemurafenib			Versus dacarbazine		
Health state	QALY dabrafenib	QALY vemurafenib	Increment	% absolute increment (ignoring negatives)	QALY dacarbazine	Increment	% absolute increment
PFS	[redacted]	[redacted]	[redacted]	7	[redacted]	[redacted]	38
PPS	[redacted]	[redacted]	[redacted]	93	[redacted]	[redacted]	62
Total	[redacted]	[redacted]	[redacted]	100	[redacted]	[redacted]	100

Table 68. Incremental costs by health state (at PAS price)

		Versus vemurafenib			Versus dacarbazine		
Health state	Cost dabrafenib (£)	Cost vemurafenib (£)	Increment (£)	% absolute increment (ignoring negatives)	Costs dacarbazine (£)	Increment (£)	% absolute increment (ignoring negatives)
PFS	[redacted]	[redacted]	[redacted]	53.7	[redacted]	[redacted]	99.6
PPS	[redacted]	[redacted]	[redacted]	46.3	[redacted]	[redacted]	0.4
Total	[redacted]	[redacted]	[redacted]	100	[redacted]	[redacted]	100

Table 69. Incremental costs by category of cost (at PAS price)

		Versus vemurafenib			Versus dacarbazine		
Health state	Cost dabrafenib (£)	Cost vemurafenib (£)	Increment (£)	% absolute increment (ignoring negatives)	Costs dacarbazine (£)	Increment (£)	% absolute increment (ignoring negatives)
Medication	[redacted]	[redacted]	[redacted]	44.1%	[redacted]	[redacted]	99.3%
Administration	[redacted]	[redacted]	[redacted]	0.2%	[redacted]	[redacted]	-2.5%
Adverse Events	[redacted]	[redacted]	[redacted]	8.3%	[redacted]	[redacted]	0.9%
Testing	[redacted]	[redacted]	[redacted]	0.0%	[redacted]	[redacted]	0.4%
Other PF costs	[redacted]	[redacted]	[redacted]	1.3%	[redacted]	[redacted]	1.5%
Other PP costs	[redacted]	[redacted]	[redacted]	46.3%	[redacted]	[redacted]	0.4%
Total	[redacted]	[redacted]	[redacted]	100.0%	[redacted]	[redacted]	100.0%

Base-case analysis

7.7.6 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.

Pairwise and incremental analyses

Basecase pairwise and incremental analyses for dabrafenib versus vemurafenib and dacarbazine are presented in the tables below incorporating the dabrafenib patient access scheme. Results using the dabrafenib list price are presented in Appendix 10.23.

Table 70. Dabrafenib monotherapy vs. vemurafenib and dacarbazine

A: Pairwise analyses incorporating PAS

	Dabrafenib	Dacarbazine	Vemurafenib	Dabrafenib vs. Dacarbazine	Dabrafenib vs. Vemurafenib
Effectiveness, Discounted					
Progression-Free Life Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-Progression Life Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quality-Adjusted Life Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs, Discounted					
Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diagnostic Testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other, Progression-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other, Post-Progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-Effectiveness					
Cost per Progression-Free Life Year				100,204	122,046
Cost per Life Year				34,962	7,531
Cost per Quality-Adjusted Life Year				49,019	11,028

B: Incremental analyses (incorporating PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Inc LYG	Inc QALYs	ICER (£) vs baseline (QALYs)	ICER (£) incremental (QALYs)
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	60,980	Extended dominance
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,019	49,019

Assessment of interventions under NICE's criteria for life-extending, end of life medicines

In respect of the comparison versus dacarbazine, dabrafenib meets criteria as a life-extending, end of life therapy, fulfilling the specific criteria in relation to this as set out in NICE's Supplementary Advice (2009) on end of life (EoL) medicines.

(i) The treatment is indicated for patients with a short life expectancy, normally less than 24 months

BRIM-3 suggests a median overall survival in vemurafenib-treated patients of 13.2 months (December 2010 datacut).[38] The survival of patients treated with dacarbazine is poorer (9.6 months).[38] An updated OS analysis from BRIM-3 (February 2012) confirms this: median OS: 13.6 months with vemurafenib vs. 9.7 months with dacarbazine.[84] Despite advances in treatment for patients with metastatic melanoma, life expectancy is still short and this remains a group with a need for life-extending therapies.

(ii) The treatment is licensed, or otherwise indicated, for small patient populations

Advanced/metastatic melanoma patients represent a small population, only approximately half of whom will be eligible for the targeted agents under consideration here. We estimate this to be a maximum of 990 per annum in England and Wales (a figure consistent with the estimate provided by the manufacturer of the number of patients potentially eligible for treatment with vemurafenib in the same indication) (see Section 2.2).

(iii) The treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

Median OS for each treatment (Table 71) estimated using the log-normal and AJCC survival extrapolations employed in the economic evaluation for this submission, confirm that dabrafenib offers an extension to life of at least 3 months in comparison with dacarbazine.

Table 71. Incremental median OS for dabrafenib vs. dacarbazine

Treatment	Median OS (months)	Increment vs. dacarbazine
Dabrafenib monotherapy	21.0	7.5
Dacarbazine	13.5	-

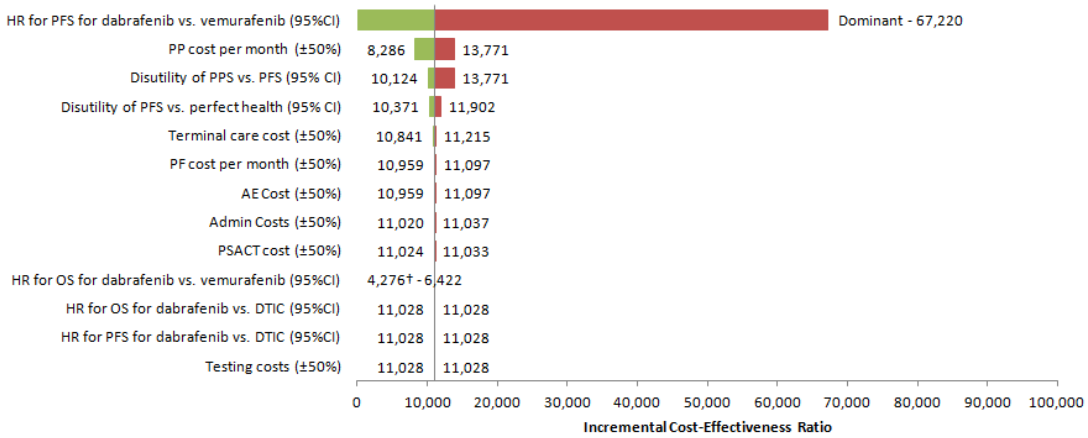
Sensitivity analyses

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

The following tornado plots for dabrafenib (PAS price) versus dacarbazine and vemurafenib summarise key results of the deterministic sensitivity analyses (where there is an underlying range of values being assessed). The tables presenting the full results of DSA where modelling assumptions are changed one at a time are reported below (analyses that considerably impact results are shaded in Table 72). These analyses are re-run using the dabrafenib list price and the results are presented in Appendix **Error! Reference source not found.**

Figure 16. Tornado plot analyses (PAS price)

A. Dabrafenib vs. vemurafenib



B. Dabrafenib vs. dacarbazine

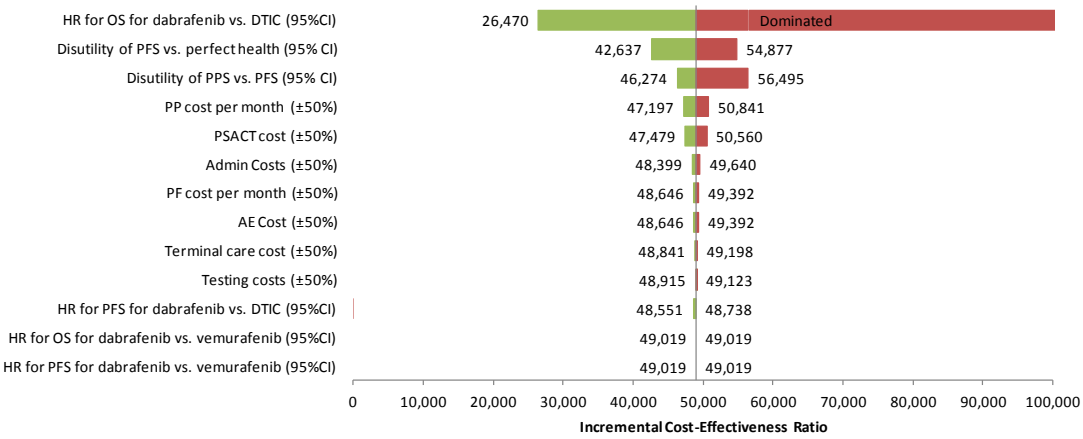


Table 72. Results of deterministic sensitivity analyses on cost-effectiveness of dabrafenib vs. vemurafenib and dacarbazine (incorporating PAS)

		Strategies						Dabrafenib vs.					
		Dabrafenib		Dacarbazine		Vemurafenib		Dacarbazine			Vemurafenib		
		QALYs	Cost	QALYs	Cost	QALYs	Cost	QALYs	Cost	Cost/QALY	QALYs	Cost	Cost/QALY
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,019	[redacted]	[redacted]	11,028
1	Time horizon set to 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68,520	[redacted]	[redacted]	13,464
2	BRAF class effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,019	[redacted]	[redacted]	Dominated
3	PFS for dabrafenib and dacarbazine – Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,759	[redacted]	[redacted]	Dominant
4	PFS for dabrafenib and dacarbazine – gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,597	[redacted]	[redacted]	Dominant
5	PFS for dabrafenib and dacarbazine KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,820	[redacted]	[redacted]	25,112
6	OS for dabrafenib - Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,050	[redacted]	[redacted]	16,723
7	OS for dabrafenib - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,360	[redacted]	[redacted]	12,522
8	OS for dabrafenib - gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,104	[redacted]	[redacted]	9,754
9	OS for dabrafenib based on Kaplan-Meier data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,573	[redacted]	[redacted]	8,951
10	OS for dacarbazine (trial segment) based on RPSFT-adjusted Kaplan-Meier data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,808	[redacted]	[redacted]	11,028
11	OS for dacarbazine (trial segment) based on proportional hazards versus dabrefnib using ITT HR from BREAK-3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95,225	[redacted]	[redacted]	11,028

12	Survival for dacarbazine based on AJCC survival for entire model timeframe, dabrafenib and vemurafenib based on proportional hazards vs. dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,180	[redacted]	[redacted]	11,592
13	Survival for dacarbazine and vemurafenib based on approach taken for vemurafenib NICE submission, dabrafenib based on proportional hazards vs. vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,802	[redacted]	[redacted]	8,993
14	HR for PFS for dabrafenib vs. dacarbazine (lower CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,551	[redacted]	[redacted]	11,028
15	HR for PFS for dabrafenib vs. dacarbazine (upper CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,738	[redacted]	[redacted]	11,028
16	HR for PFS for dabrafenib vs. vemurafenib (lower CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,019	[redacted]	[redacted]	67,220
17	HR for PFS for dabrafenib vs. vemurafenib (upper CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,019	[redacted]	[redacted]	Dominant
18	HR for OS for dabrafenib vs. dacarbazine (lower CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,470	[redacted]	[redacted]	11,028
19	HR for OS for dabrafenib vs. dacarbazine (upper CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	11,028
20	HR for OS for dabrafenib vs. vemurafenib (lower CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,019	[redacted]	[redacted]	6,422

21	HR for OS for dabrafenib vs. vemurafenib (upper CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,019	[redacted]	[redacted]	4,276 †
22	Perfect dose intensity for all comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,210	[redacted]	[redacted]	10,956
23	Admin costs set to +50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,399	[redacted]	[redacted]	11,037
24	Admin costs set to -50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,640	[redacted]	[redacted]	11,020
25	PF costs set to +50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,392	[redacted]	[redacted]	11,097
26	PF costs set to -50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,646	[redacted]	[redacted]	10,959
27	PP costs set to +50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,841	[redacted]	[redacted]	13,771
28	PP costs set to -50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,197	[redacted]	[redacted]	8,286
29	Testing costs set to +50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,123	[redacted]	[redacted]	11,028
30	Testing costs set to -50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,915	[redacted]	[redacted]	11,028
31	PSACT cost set to +50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,479	[redacted]	[redacted]	11,024
32	PSACT cost set to -50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,560	[redacted]	[redacted]	11,033
33	PSACT cost set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	52,100	[redacted]	[redacted]	11,038
34	Terminal care cost set to +50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,841	[redacted]	[redacted]	10,841
35	Terminal care cost set to -50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,198	[redacted]	[redacted]	11,215

36	Costs of all AEs simultaneously set to +50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,239	[redacted]	[redacted]	11,485
37	Costs of all AEs simultaneously set to -50% of base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,800	[redacted]	[redacted]	10,571
38	Set cost of all adverse events to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,580	[redacted]	[redacted]	10,115
39	Disutility of PFS vs. perfect health set to -50% of the base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,090	[redacted]	[redacted]	13,299
40	Disutility of PFS vs. perfect health set to +50% of the base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,698	[redacted]	[redacted]	9,420
41	Disutility of PPS vs. PFS for dacarbazine assumed to be same as Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,343	[redacted]	[redacted]	11,028
42	Disutility of PPS vs. PFS set to -50% of the base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,998	[redacted]	[redacted]	11,751
43	Disutility of PPS vs. PFS set to -50% of the base case value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,363	[redacted]	[redacted]	10,389

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

In PSA analysis, dabrafenib monotherapy (PAS price) is cost effective versus vemurafenib in 56% of cases at a £30,000/QALY threshold and in 6% of cases versus dacarbazine. At a higher threshold of £50,000/QALY (which is relevant for its comparison versus dacarbazine), dabrafenib is cost-effective versus dacarbazine in 43.5% of cases. These analyses are re-run using the list price for dabrafenib and are presented in Appendix **Error! Reference source not found.**.

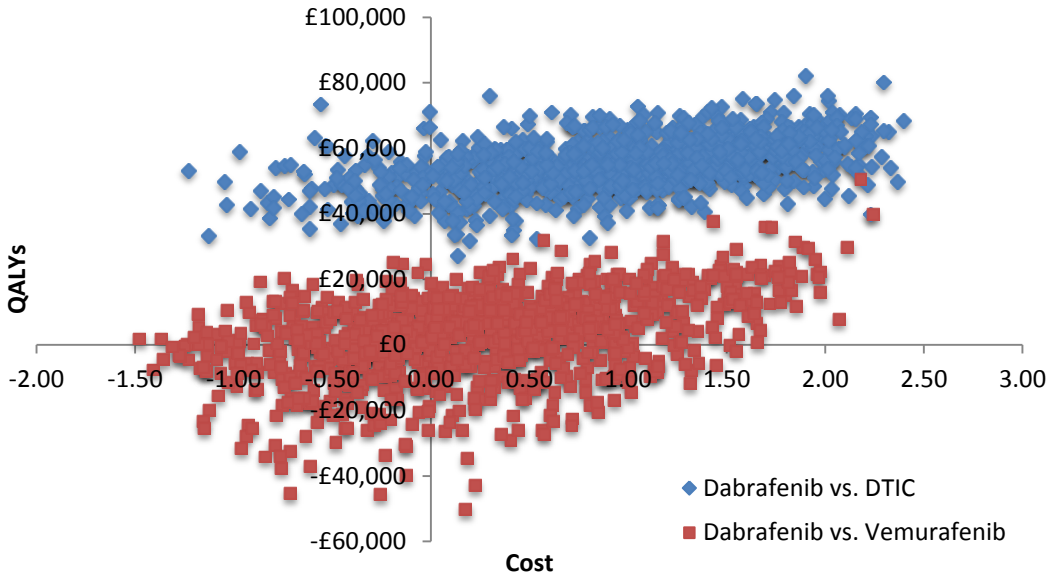


Figure 17. Plot of incremental costs and incremental QALYs for dabrafenib vs. vemurafenib and dacarbazine from PSA

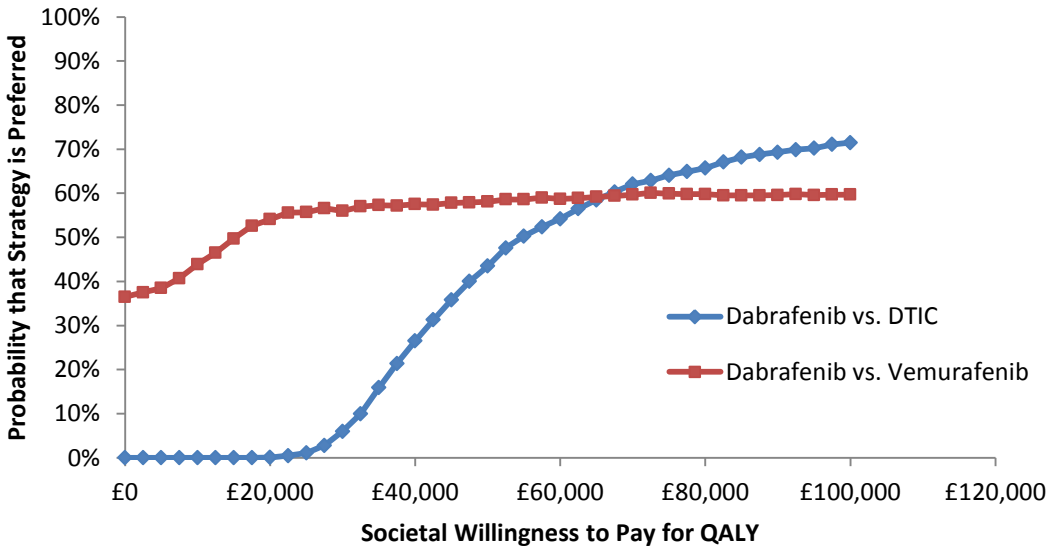


Figure 18. Acceptability curves for pairwise comparisons for dabrafenib vs. vemurafenib and dacarbazine

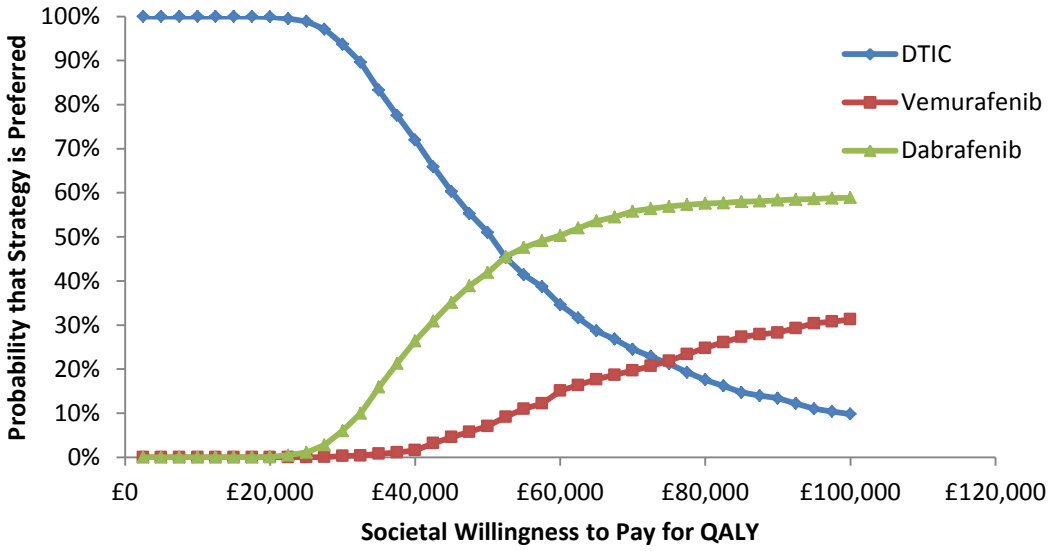


Figure 19. Acceptability curves for incremental analysis of dabrafenib vs. vemurafenib and dacarbazine

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

The full deterministic sensitivity analyses, including results of structural sensitivity analyses, are presented in Section 7.7.7.

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

The findings of the probabilistic sensitivity analyses for the base case (incorporating the PAS for dabrafenib) are discussed above and summarised in the tables below.

Table 73. Summary of PSA for dabrafenib (PAS price)

QALY threshold	Probability that dabrafenib monotherapy is cost-effective versus comparator (%)	
	Vemurafenib	Dacarbazine
£30,000	56%	6%
£50,000	*NR*	43.5%

At its discounted price, dabrafenib was cost effective at a threshold of £30,000/QALY versus vemurafenib in 56% of cases. Versus dacarbazine, dabrafenib was cost-effective at a threshold of £50,000/QALY in 43.5% of cases.

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

For the comparison versus vemurafenib the analysis is most sensitive to assumptions regarding PFS. PFS determines the duration of treatment and given [redacted] this is the key driver of incremental costs. Varying assumptions for vemurafenib PFS according to the lower and upper bounds of the CI for the HR from the indirect treatment comparison, results in ICERs ranging from £67,220 to a scenario where dabrafenib dominates vemurafenib. The comparison versus vemurafenib is also sensitive to assumptions regarding OS, where using the lower and upper bounds of the confidence interval around the indirect treatment comparison, result in ICERs ranging from £6,422 to a scenario where dabrafenib is less costly but less effective than vemurafenib (SW quadrant). Where a class effect for vemurafenib and dabrafenib is assumed, dabrafenib has equal QALYs but marginally higher costs than vemurafenib [redacted] This small difference in costs is associated with differences in the cost of treating adverse events.

OS is the key driver of cost-effectiveness for dabrafenib versus dacarbazine. Incorporating the lower or upper bound of the confidence interval for the OS HR in BREAK-3 (RPSFT-adjusted) results in ICERs ranging from £26,470 to dabrafenib being dominated by dacarbazine.

7.8 Validation

7.8.1 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 dabrafenib economic model was developed by Policy Analysis Incorporated (PAI). The Excel workbook used for this evaluation was validated internally by PAI and by the York Health Economics Consortium (YHEC). PAI's validation was done by taking the inputs to the model and entering them into an older model, also developed by PAI, which has been used in prior economic evaluations and which has been validated by both the Programs for Assessment of Technology in Health (PATH) Research Institute and EcoStat Consulting UK Ltd. Since the older model used for validation is not capable of modelling survival using time-dependent hazards ratios, calculations of progression-free survival and overall survival by week could not be validated and were input directly into the validation model. Results for the validation of model results showed no material differences in measure of costs or effectiveness between the model used in this evaluation and the validation model (i.e., difference between models <0.002% for all measures). No material differences between the results generated by the PAI model and the YHEC validation model were identified.

The model validated by YHEC was produced for the Canadian health care system. The model has subsequently been updated with UK specific data for this appraisal.

7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken andhow these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost-effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

We do not present any subgroup analyses in the economic modeling. However, the population under consideration here are previously untreated patients with $BRAF^{V600}$ mutation-positive metastatic melanoma, a subgroup of the licence which does not specify a line of therapy.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

N/A

7.9.3 Please describe how the statistical analysis was undertaken.

N/A

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

N/A

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

The scope specified separate consideration of previously treated patients. However, there is insufficient evidence from current clinical trials with which to build an economic argument for dabrafenib in this subgroup of patients.

Additionally, the scope distinguishes people whose malignant melanoma has metastasised to the brain. However, there is insufficient evidence from the BREAK-MB study of dabrafenib in patients with melanoma that has metastasised to the brain with which to build an economic argument. BREAK-3 did not exclude patients with brain metastases (although patients with brain lesions were confirmed stable) and from a staging perspective, patients with distant brain metastases are not currently distinguished from other metastatic sites. The clinical relevance of making a separate

economic case for such patients is therefore questionable given the broad licence for dabrafenib.

There are no other obvious subgroups that have been excluded.

7.10 Interpretation of economic evidence

7.10.1 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?

The systematic review of the economic literature did not identify any published studies assessing the cost-effectiveness of dabrafenib so it is not possible to make comparisons with published economic literature.

However, vemurafenib was assessed by NICE in December 2012 and the Appraisal Committee accepted that ICERs for vemurafenib vs. dacarbazine were likely to range between £44,000 - £51,800/QALY (See Appendix **Error! Reference source not found.**). In the current evaluation, the ICER for vemurafenib vs. dacarbazine is £60,980. However when a class effect for the BRAF inhibitors is assumed, the ICER for vemurafenib versus dacarbazine is £48,800. This is consistent with the range of ICERs reported in the the vemurafenib appraisal. The similarity in these estimates provides some reassurance about the model structure and provides a face validity check for the one that underpins the current assessment.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Dabrafenib is already licensed by the EMA for the treatment of adult patients with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation whereas treatment-naive patients are the main focus of this submission.

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

Strengths	An assessment of this economic analysis on the basis of the critical appraisal checklist by Drummond and Jefferson, Philips and colleagues, and the NICE reference case[128,129] is provided in Appendix **Error! Reference source not found.**. This assessment meets all of these standard quality criteria. In addition: • The economic analysis utilises an established modelling methodology used in previous assessments of medicines for patients with metastatic melanoma • Parametric distributions of OS from BREAK-3 were combined with case-mix adjusted survival data from the AJCC melanoma registry, assuming no additional benefit for dabrafenib beyond the follow-up of the trial. AJCC data arguably represent the best source of long term survival data for patients with metastatic melanoma receiving standard treatment and therefore add external validity to the model

	projections (survival estimates from the AJCC melanoma are similar to those for Stage IV melanoma patients from SEER that was used by the manufacturer in the economic evaluation of vemurafenib for NICE). • The assumption of no additional benefit beyond the maximum follow-up for dabrafenib may result in a conservative estimate of the benefit of dabrafenib. • Approaches previously endorsed by the Appraisal Committee in the assessment of vemurafenib (namely the piecewise approach to modelling and use of observational data to facilitate extrapolation) were adopted in this assessment giving it face validity. • In the absence of head-to-head data, the analyses for comparative efficacy utilise the adjusted indirect treatment comparison methodology (Bucher et al), as recommended by NICE, to maintain randomisation across studies. • Parametric survival curves are selected on the basis of a comprehensive assessment of goodness of fit. • The model predicts clinical outcomes that are comparable or conservative compared to those seen in clinical trials. This gives reassurance that the predicted benefit of dabrafenib is not overestimated. • The model accounts for the costs of post-study anti-cancer therapy. • The model incorporates a comprehensive range of scenario analyses in DSA. • Utility data were derived for dabrafenib directly from phase III studies in $BRAF^{V600}$ mutation-positive metastatic melanoma patients being treated with targeted therapies; this eliminates the need to model impact of AEs as these are already captured in the underlying study.
Limitations	Certain limitations must be acknowledged: • The pivotal trials for dabrafenib and vemurafenib permitted crossover of control group patients to the experimental arm upon progression; accordingly all have confounded OS results and required that these be adjusted before being utilised in ITCs or modelling. • Cross over adjustments were as comprehensive as possible, however, the IPCW approach was not attempted as there were insufficient data from the studies (in particular there were too few control patients who had died without crossing over). • In the absence of head-to-head data for dabrafenib versus vemurafenib, ITCs were undertaken which by definition require an assumption of proportional hazards to be implemented in modelling; this assumption may not hold (and which may result in survival distributions that do not match those of the trials from which the HRs were derived). There is some evidence of this in the divergence of the model-predicted OS distribution for dacarbazine (see Section 7.7.1) with that observed for dacarbazine in BREAK-3, however the overall

	impact is likely conservative. The proportional hazards assumption is discussed in further detail in Section 7.3.1.

Not uncommon in economic models of oncology treatments, uncertainty in this analysis is linked to the overall survival results in the underlying studies of the interventions. Largely for ethical reasons, BREAK-3 permitted cross over of patients from the control arm to the intervention arm upon progression. As a result the overall survival results are confounded and the incremental benefit of dabrafenib is underestimated. The RPSFT methodology which was applied to adjust this dataset for this effect preserves the p-value from the underlying trial and as a consequence a non-significant OS result (which may be largely due to the effects of crossover) can never become significant under this methodology.

In spite of the uncertainty in the underlying overall survival data, the model predicts PFS and OS results that are largely consistent with those see in clinical data. Where the estimates are not comparable, i.e. OS for dacarbazine and vemurafenib, the impact is likely a conservative one, see Section 7.7.1.

GSK is seeking a recommendation for dabrafenib as an alternative to vemurafenib for the treatment of adult patients with $BRAF^{V600}$ mutation-positive metastatic melanoma. A recommendation for dabrafenib would provide patients and clinicians with a choice of BRAF inhibitor. Dabrafenib offers similar efficacy and a different side effect profile [redacted]

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

This evaluation is based on indirect evidence for dabrafenib versus vemurafenib. A head to head RCT versus vemurafenib would reduce the uncertainty associated with the estimates of cost-effectiveness.

Future datacuts of OS from BREAK-3 (where the duration of follow up is similar to that in BRIM-3) will improve the reliability of the indirect treatment comparison and the certainty of the results presented here.

Comprehensive sensitivity analyses provided here, both PSA and DSA, assess the impact of varying assumptions on the cost-effectiveness result and should provide a reasonable set of results with which to respond to the current decision problem.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 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.

We estimate the incident population of adults with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation to be approximately 990 per annum. The estimate is detailed in Section 2.2 and represents the maximum total population to whom this therapeutic indication refers.

Assuming a population growth of 0.8% per annum, the maximum total eligible population over the next five years is represented in Table 74. This estimate does not account for market share and so represents a maximum number of eligible patients.

Table 74. Maximum eligible population

Year	2015	2016	2017	2018	2019
Maximum eligible population	990	998	1006	1014	1022

Assumes 8% growth per annum

Table 75. Likely patient numbers (with market share and uptake assumptions)

Year	2015	2016	2017	2018	2019
85% tested	842	848	855	862	869
90% suitable for 1L treatment	757	763	770	776	782
75% receive 1L targeted therapy	568	573	577	582	586
Anticipated patients with market share assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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

Table 75 above assumes:

- 85% of all $BRAF^{V600}$ mutation-positive patients are tested
- 90% of them are suitable for first line treatment
- 75% receive a 1L targeted agent
- Market share assumptions are provided in Table 75.

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

Market share assumptions are provided in Table 75.

8.4 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).

All relevant costs associated with these technologies are incorporated into the budget impact estimates below (which are derived from the economic model) and represent total costs to the NHS assuming that the patient access schemes are implemented.

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

Treatment costs are derived from the economic model and are provided in Table 76; cost inputs are described in detail in Section 7.5.5.

Table 76. Costs derived from the economic model and used in budget impact calculations

	Dabrafenib cost/patient	Vemurafenib cost/patient
Drug acquisition / patient	[redacted]	[redacted]
Testing / patient treated	[redacted]	[redacted]
Administration / patient	[redacted]	[redacted]
Treatment of adverse events / patient	[redacted]	[redacted]
Other pre-progression costs / patient	[redacted]	[redacted]
Total costs	[redacted]	[redacted]

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

Vemurafenib is the current standard of care for patients with $BRAF^{V600}$ metastatic melanoma. It too is a targeted therapy and patients are identified in a comparable way to that expected for dabrafenib. We do not anticipate the introduction of dabrafenib to result in considerable resource savings compared to the requirements for vemurafenib.

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

Table 77 below describes the anticipated 5 year budget impact to the NHS of introducing dabrafenib, assuming positive NICE guidance and incorporating the patient access scheme for dabrafenib. Underlying patient estimates are as described in Table 75 above and it is assumed that these costs will displace those of vemurafenib, not be in addition to them.

Table 77. Anticipated budget impact of introducing dabrafenib

	2015	2016	2017	2018	2019
Current practice					
Vemurafenib market share	100%	100%	100%	100%	100%
Vemurafenib patients	568	573	577	582	586
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Future practice					
Vemurafenib market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The budget impact presented in Table 77 is based on costs taken from the economic base case. If a class effect for BRAF inhibitors is assumed [redacted]

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

None.

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