NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma

This premeeting briefing presents:

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

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The scope defined dabrafenib monotherapy and vemurafenib monotherapy as the comparators, therefore the company did not include pembrolizumab or ipilimumab. However, expert advice to the ERG considered that in clinical practice many BRAF mutation positive patients (up to 70%) would be treated with an immunotherapy first line before switching to a BRAF inhibitor and a MEK inhibitor.
  - Where are the BRAF inhibitors currently used in the treatment pathway?
- Since the scope was issued by NICE for the appraisal of cobimetinib + vemurafenib, trametinib in combination with dabrafenib has been appraised by

NICE and a final appraisal determination has been issued recommending trametinib. This decision is subject to appeal and it is anticipated that guidance would be issued in [redacted]. Nivolumab has also been recommended in February 2016 for people with melanoma with and without the BRAF V600 mutation.

  - Has the treatment pathway for unresectable or metastatic melanoma changed since the scope for cobimetinib + vemurafenib was issued in August 2015?

- The clinical effectiveness data comes from one trial, coBRIM, of people with previously untreated unresectable or metastatic BRAF V600 mutation-positive melanoma. However, the marketing authorisation for cobimetinib + vemurafenib and the population defined in the scope are not limited to previously untreated patients. The ERG states that there are no data available to suggest the outcomes would be worse if cobimetinib + vemurafenib are used as a second line treatment.
  - What is the committee's view on the expected place of the combination treatment in the treatment pathway?
  - Are the results from the trials generalisable to a second line setting?
  - Would the BRAF agents be expected to have the same efficacy after failure of immunotherapy as first line, and would the relative benefit of adding cobimetinib to a BRAF agent be the same second line as first line?
- The ERG highlighted uncertainties with the coBRIM trial based on randomisation and allocation concealment procedures and a potential risk of attrition bias favouring the cobimetinib + vemurafenib group.
  - What is the committee's view of the coBRIM results?
- What proportion of people would be expected to take cobimetinib + vemurafenib at a lower dosage than that stated in the marketing authorisation in clinical practice in England? Is coBRIM generalisable to clinical practice in this regard?
- What proportion of people would be expected to stop cobimetinib + vemurafenib before disease progression in clinical practice in England? Is coBRIM generalisable to clinical practice in this regard?
- Is PFS an appropriate surrogate marker for time on treatment?
- What is the committee's view on the adverse event and quality of life data collected in the coBRIM trial?

- The company undertook a network meta-analysis to estimate the clinical effectiveness of cobimetinib in combination with vemurafenib compared with dabrafenib monotherapy. The evidence network was sparse and clinical heterogeneity between the trials was not discussed.
  - What is the committee's view of the reliability of these data for this comparison?
  - Are vemurafenib and dabrafenib considered to be clinically equivalent in clinical practice?

Cost effectiveness

- The company did not present a fully incremental analysis because it noted data limitations did not allow it to estimate time on treatment for dabrafenib in the same way as it did for cobimetinib + vemurafenib and vemurafenib. Was this appropriate?
- What is the committee's view on the most reasonable approach to model time on treatment? Is it appropriate to use different approaches in different modelled treatment arms?
- Model results are sensitive to the parametric curves chosen to extrapolate beyond the coBRIM trial data for PFS, OS and time on treatment. The company chose the parametric curve in its base case based on best statistical fit to the trial data. Which curves provide the most clinically plausible extrapolation?
- Are there people with progressed disease who are considered to have 'stable progressed disease'? If so how does this effect:
  - the prognosis for these people in terms of survival
  - quality of life and
  - do treatment costs differ from people with non-stable progressed disease?
  - How should stable progressed disease be defined?
- The company have stated that if it were to set the cost of cobimetinib to £0, the ICER for cobimetinib + vemurafenib compared with the comparators outlined in the final scope issued by NICE would be above that normally considered a cost effective use of NHS resources by NICE and as such illustrates an issue with the NICE methods for technology appraisal. What are the committee's views on this?

Other

- Does the committee consider cobimetinib in combination with vemurafenib meets the NICE methods guide end of life criteria?
- Does the committee consider cobimetinib to be an innovative therapy?
- Are there any uncertainties surrounding the clinical effectiveness of cobimetinib + vemurafenib that would warrant continued follow up of cobimetinib + vemurafenib within the new CDF framework?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of cobimetinib in combination with vemurafenib within its marketing authorisation for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Pop.	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma	
Int.	Cobimetinib in combination with vemurafenib	
Com.	• dabrafenib • vemurafenib	
Out.	• progression free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life	

1.2 The ERG commented on the population:

- Trial population (on which clinical and cost effective estimates were based) only included people who had no prior treatment
- Clinical advice to the ERG was that some patients (estimated up to 70%) with advanced (unresectable or metastatic) BRAF mutation

positive melanoma would receive immunotherapy as a first line treatment (e.g. ipilimumab, pembrolizumab, or nivolumab), before potentially switching to a BRAF mutation inhibitor. The ERG stated that a BRAF inhibitor might be a more commonly used first line treatment for BRAF mutation positive patients with a higher burden of disease or faster disease progression because it may be faster acting than some immunotherapies.

- Clinical advice to the ERG was that the efficacy and safety of cobimetinib + vemurafenib in people who had prior immunotherapy would be similar to people who had not had previous treatment.

1.3 ERG commented on comparators:

- Comparators in submission correspond to NICE scope
  - notes ipilimumab and pembrolizumab as potential comparators because these are now recommended by NICE to treat advanced melanoma, including BRAF mutation positive melanoma.
- Alternative BRAF inhibitor and MEK inhibitor combination (dabrafenib + trametinib) is currently being appraised by NICE in a separate appraisal (ID661) *NB this went straight to FAD with a positive recommendation and the FAD was sent to consultees for appeal 22/4/16 .According to current NICE timelines the anticipated date of guidance publication would be* [redacted]

2 The technology and the treatment pathway

2.1 Melanoma is a cancer of the skin. In its early stages, melanoma is normally asymptomatic and can often be cured by surgery (resection). However, it can spread or metastasise to nearby lymph nodes (stage III) or to other parts of the body (stage IV). Most melanomas occur in people with pale skin. The risk factors are skin that tends to burn in the sun, having many moles, intermittent sun exposure and sunburn. A mutated form of the BRAF gene (called BRAF V600) is found in about 50% of melanomas. The mutated gene means that the cells produce too much

BRAF protein, leading to uncontrolled cell division and growth of the tumour.

2.2 Cobimetinib is a MEK inhibitor, it inhibits MEK 1/2 (a signalling protein in the same signalling pathway as BRAF). Inhibiting MEK 1/2 blocks cancer cell proliferation and survival. The company states that inhibiting two proteins in the signalling pathway results in stronger inhibition and decreased tumour cell proliferation. It also overcomes resistance to BRAF inhibition by vemurafenib

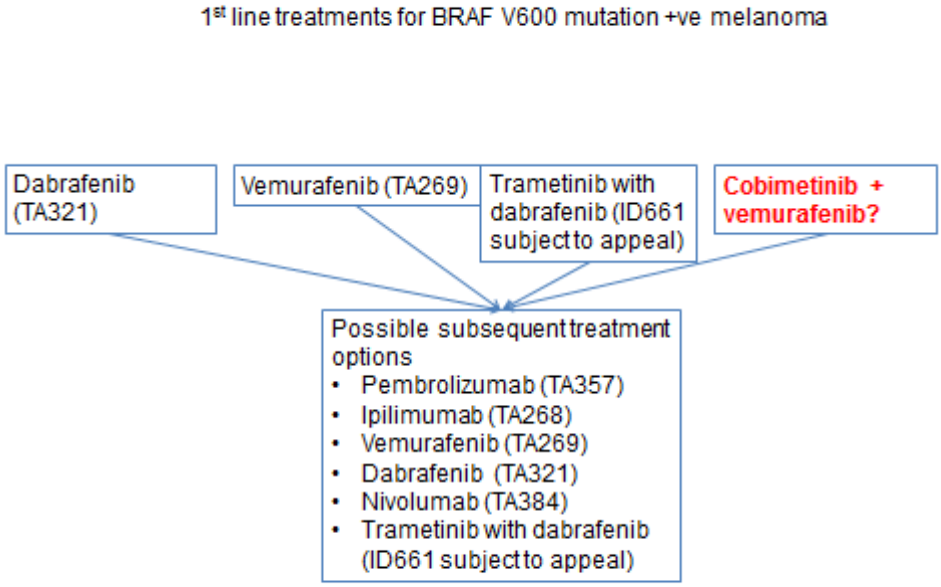
2.3 Treatments for advanced (unresectable or metastatic) melanoma fall into 2 groups. Those that are targeted for people who have BRAF V600 positive tumours (cobimetinib, trametinib + dabrafenib (subject to ongoing technology appraisal ID661), vemurafenib and dabrafenib) and those that can be used independently of BRAF mutation status (ipilimumab, pembrolizumab, nivolumab). Testing for BRAF V600 is standard for people with melanoma. Although ipilimumab, pembrolizumab or nivolumab may be used as a first line treatment in some people with BRAF mutations whose disease is not progressing rapidly and who are relatively fit, BRAF inhibitors are the preferred first treatment for people with BRAF V600 mutations. A summary of NICE technology appraisal guidance recommending technologies for unresectable or metastatic melanoma is given in table 1 below and a schematic of the treatment options in figure 1.

Table 2: NICE technology appraisal guidance for unresectable metastatic melanoma

NICE guidance	population
TA384 (Feb 2016) Nivolumab	Adults with advanced (unresectable or metastatic) melanoma
TA366 (Nov 2015) Pembrolizumab	Adults with advanced (unresectable or metastatic) melanoma not previously treated with ipilimumab
TA357 (Oct 2015) Pembrolizumab	Adults with unresectable or metastatic melanoma whose disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease a BRAF or MEK inhibitor
TA 319 (Jul 2014) Ipilimumab	Adults with previously untreated advanced (unresectable or metastatic) melanoma

TA321 (Oct 2014) dabrafenib	Adults with unresectable or metastatic V600 mutation positive melanoma
TA268 (Dec 2012) Ipilimumab	People with advanced (unresectable or metastatic melanoma in people who have received prior therapy
TA 269 (Dec 2012 updated Jan 2015) vemurafenib	People with BRAF V600 mutation-positive unresectable or metastatic melanoma

Figure 1: schematic of NICE TA recommendations for unresectable of metastatic melanoma.



1st line treatments for unresectable or metastatic melanoma (not specific for melanoma with BRAF V600 mutation)

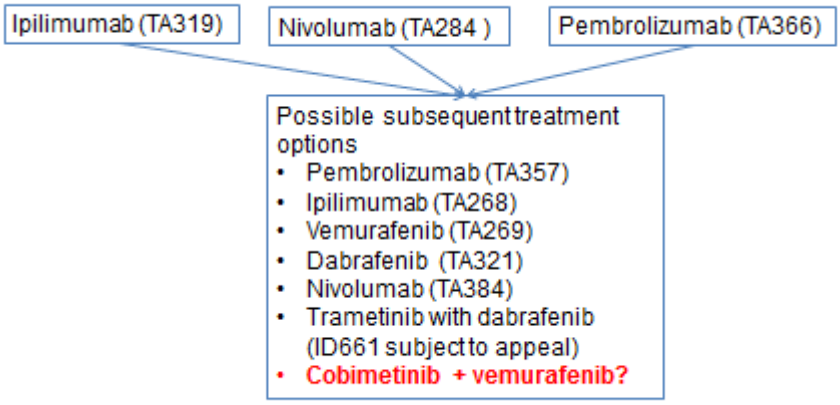


Table 3 Technology

	cobimetinib	**vemurafenib**	**dabrafenib**	**For information only trametinib (taken with dabrafenib)**
Marketing authorisation	Cobimetinib is indicated for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	Dabrafenib as monotherapy or in combination with trametinib* is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation * In combination with trametinib is an extension to the MA	
Administration method	Oral 20 mg tablet Recommended dose 60 mg (3 tablets of 20 mg) once daily. It is taken in a cycle of 28 days (21 days taking treatment and a 7 day break). Patients should remain on treatment until disease progression or unacceptable toxicity	Oral 240 mg tablet Recommended dose of vemurafenib is 960 mg (4 tablets 240 mg) twice daily (total daily dose 1,920 mg)	Oral 75 mg capsule Recommended dose of dabrafenib, 150 mg twice daily (corresponding to a total daily dose of 300 mg)	2 mg once daily (with dabrafenib)
Cost information	£4275.67 (per pack); £4645.06 (per month) and £1425.22 per week for the 3 weeks per cycle a patient is	A patient access scheme is in place for vemurafenib. The list price cost is £1750 for 56 x 250 mg tablets (1 week's supply)	A patient access scheme is in place for dabrafenib. The list price cost is £1400 for 28 x 75 mg tablets (1 week's supply)	

	receiving cobimetinib)			

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 A submission was received from one professional organisation. It said:

- First line treatment options used in clinical practice are vemurafenib, dabrafenib and ipilimumab. Pembrolizumab is used as a subsequent treatment.
- BRAF inhibitors have around a 50% response rate and are associated with a progression free survival of around 7 months. Ipilimumab and pembrolizumab have lower response rates (15-20% and 30-40% respectively) but for those people who benefit the response can be more durable lasting some years.
- The side effects of cobimetinib in combination with vemurafenib are very similar to those of vemurafenib alone. The ocular toxicity observed with cobimetinib was of low severity and can be managed with dose modification of cobimetinib.
- The monitoring needed while taking cobimetinib with vemurafenib is likely to be similar to that needed for vemurafenib alone.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 CoBRIM was a randomised blinded (patient, sponsor, investigator) trial comparing cobimetinib + vemurafenib with vemurafenib monotherapy. The trial was multinational (11 UK centres enrolled a total of 29 patients). The trial included 495 people:

- with BRAF V600 mutation-positive unresectable locally advanced (stage IIIc) or metastatic melanoma (stage IV)
- who had no prior systemic therapy for advanced disease
- with An Eastern Cooperative Oncology Group performance status score of 0/1

For a full list of eligibility criteria please see tables 9 and 10 page 45 of company submission. The baseline characteristics of the study population are summarised in table 14 page 59 of the company submission. Of note the median age was around 55 to 56 years.

4.2 The dosing schedule was the same as the marketing authorisation (table 3). People carried on taking their assigned treatment until disease progression, unacceptable toxicity or withdrawal of consent. After stopping the study treatment people continued to be followed for survival estimates. During this time people could have other anti-cancer therapies (table 27 company submission page 99).

4.3 The primary endpoint was progression free survival (conducted on 9 May 2014). Progression free survival was defined as "time from randomisation to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever came first." Secondary outcomes included:

- Overall survival: time from randomisation to death from any cause
- Objective response rate (for patients with measurable disease at baseline); best overall response rate; duration of response. These were assessed by an investigator using RECIST v1.1 criteria. Please see page 48 of the company submission for a full definition of these criteria
- PFS based on independent review (2 board certified radiologists)
- Patient reported outcome measures: including European Organisation for Research and Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30 and the EuroQol's 5 dimension 5 level (EQ-5D-5L).

All clinical efficacy analyses were carried out in the intention-to-treat population. Patient reported outcomes were reported for people who had a baseline assessment and at least 1 follow up assessment.

4.4 There were a number of interim analyses, these are summarised in table 8 page 42 of the company submission. For how these analyses were pre-specified see page 50 company submission. Key analyses included:

- May 2014. Primary analysis date, pre-specified based on 206 events (>95% power to detect an improvement in PFS).
- January 2015. Not pre-specified, requested by EMA. Date 1 year from last patient enrolment into trial.
- August 2015. Final analysis for overall survival, pre-specified based on approximately 385 deaths (~80% power to detect improvement in OS).

ERG comments

4.5 The ERG noted:

- Small but not statistically significant differences between the study arms in terms of ECOG status at baseline, metastatic status M1c and unresectable stage IIIc. It considered that these small imbalances might be expected to favour the placebo group. Clinical expert advice to the ERG was that these differences would not influence the improvement in clinical outcomes observed with cobimetinib.
- Overall coBRIM was well designed and provides an appropriate evidence base to inform the appraisal. However there is some lack of clarity in reporting and an imbalance in drop-outs between treatment groups.
- The protocol stated that the final OS analysis should be carried out after approximately 385 deaths had occurred in order to have 80% statistical power to detect a difference between cobimetinib + vemurafenib and vemurafenib in this outcome. However only 255 events had occurred at the time of the final analysis, meaning that the analysis of overall survival was likely to be underpowered.

Clinical trial results

Table 4 Clinical trial outcomes (see company submission tables 16 page 63 and 17 page 64)

Outcome	**May 2014** **Median follow up 7.3 months (range 0.5 to 16.5 months). Pre-specified for primary outcome**		**Jan 2015** Median follow up 14.2 months		**August 2015** **Pre-specified for final overall survival analysis**	
	Cobimetinib with vemurafenib (n=247)	**Vemurafenib (n=248)**	**Cobimetinib with vemurafenib (n=247)**	**Vemurafenib (n=248)**	**Cobimetinib with vemurafenib (n=247)**	**Vemurafenib (n=248)**
Progression free survival (months) Investigator assessed, primary outcome	**9.9 (95% CI 9.0 to not reached)**	**6.2 (95% CI 5.6 to 7.4)**	12.3	7.2	Not reported	
	HR (death or disease progression) 0.51, 95% CI 0.39 to 0.68, p<0.001		HR (death or disease progression) 0.58, 95% CI, 0.46 to 0.728			
Overall survival (median, months)	Not evaluable				22.3	17.4
					HR 0.702, 95% CI 0.548 to 0.899	
Progression free survival (months) centrally assessed	11.3 (95% CI 8.5 to not reached)	6.0 (95% CI 5.6 to 7.5)	Not reported			
	HR (death or disease progression) 0.60, 95% CI 0.45 to 0.79, p<0.001					

For the response outcomes please see pages 65 to 67 of company submission. Pre-planned, exploratory analyses (small patient numbers) of subgroups based on patient characteristics are presented on pages 69 to 71 company submission. Overall subgroups consistent with ITT population results.

Figure 2. Kaplan Meier plot PFS, investigator assessed (Jan 2015) company submission figure 6 page 64

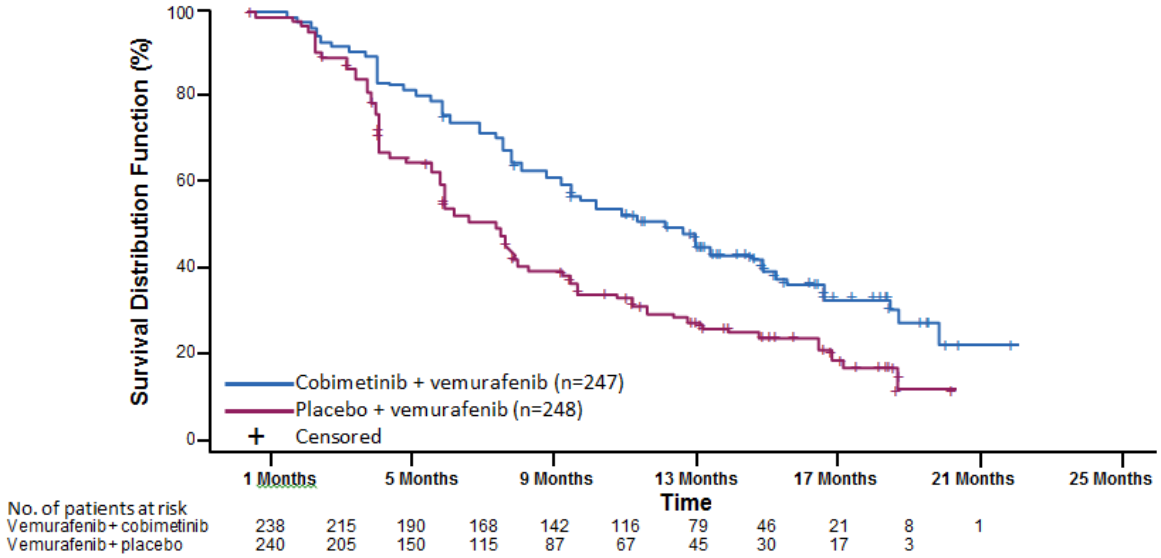
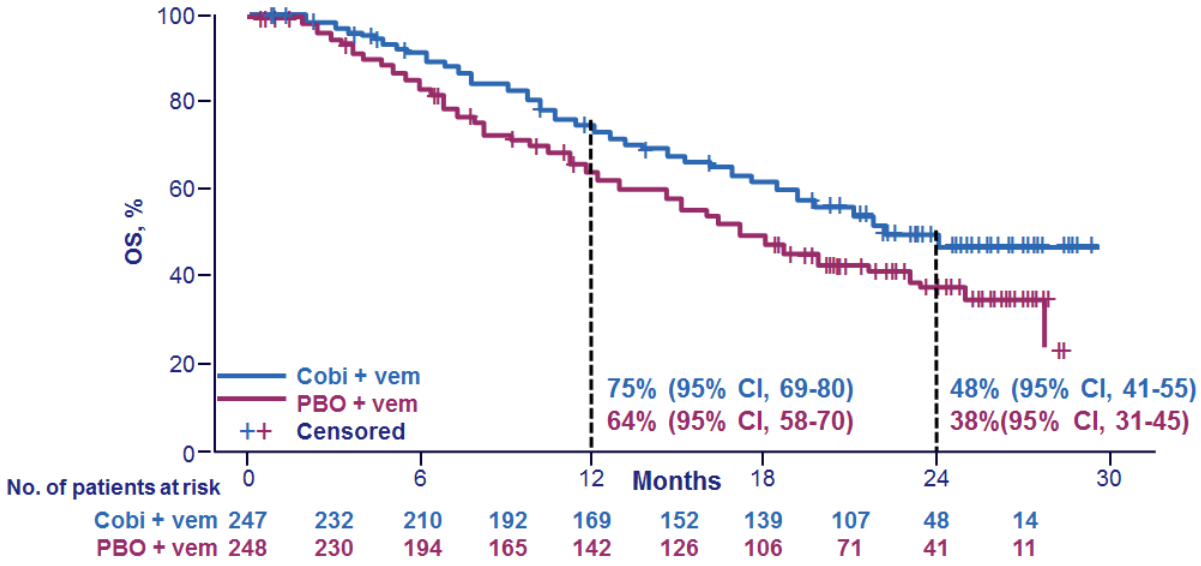


Figure 3 Kaplan-Meier OS (Aug 2015) company submission figure 7 page 65



Quality of life

4.6 The company presented data from the EORTC QLQ-C30.

- Collected day 1 and 15 in the first and second treatment cycles (28 days) and every other cycle thereafter until cycle 8 day 1 (after this time the company stated there were too few people in the vemurafenib arm to allow meaningful conclusions). There were over 88% completion rates for each assessment.
- Questionnaire was completed until withdrawal from the study or study completion. Few patients completed questionnaire after stopping their treatment because of progression so data on post disease progression quality of life is limited. (The ERG noted that it was not reported how many patients completed this questionnaire after stopping treatment and whether their responses were analysed).
- Although scores on all functioning domains (cognitive, emotional, social, role and physical) and most symptoms (appetite loss, constipation, nausea and vomiting, dyspnoea, pain, fatigue) were higher with cobimetinib + vemurafenib compared with vemurafenib

these did not meet criteria for clinically meaningful change (≥ 10 point increase or decrease from baseline).

In response to clarification (question B2 pages 20 + 21) the company presented utility values calculated from EQ-5D data for both trial arms on the 1st day of cycles 1, 2 and every other cycle thereafter until the end of the study (after cycle 22).

ERG comments on health related quality of life data.

4.7 The ERG commented that the quality of life analysis in coBRIM would be statistically underpowered for detecting differences between the trial arms. However, while people are still receiving treatment before progression there appears to be some benefit associated with cobimetinib + vemurafenib compared with vemurafenib. The ERG also noted the QLQ-C30 is widely used in cancer research studies but is not specific to skin cancer and might not be the most sensitive instrument for capturing the effects of melanoma on patients' HRQoL.

Meta-analyses/indirect comparison/MTC

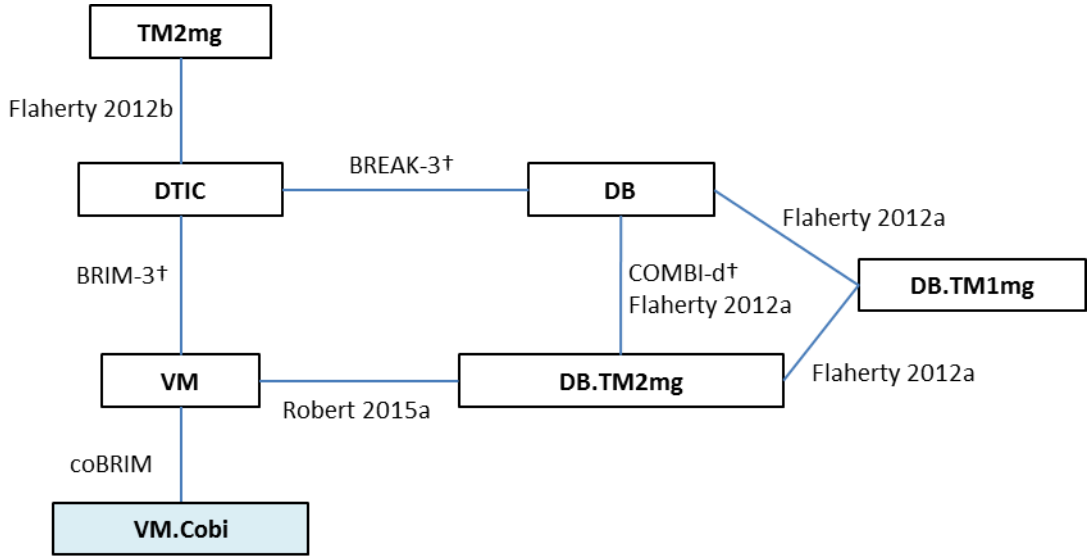
4.8 A network meta-analysis was carried out by the company to indirectly compare cobimetinib + vemurafenib with dabrafenib because there were no head-to-head trials.

- Used a Bayesian accelerated time failure (AFT) model. AFT models do not need proportional hazards. The company stated that evidence from a previously conducted NMA (Brexelius 2014) found that the AFT survival model was a better fit than the proportional hazards model for trials in metastatic melanoma.
- Used fixed effect model because it had a better statistical fit than a random effects model and company stated was more appropriate because of the small network and limited number of studies.
- Alongside dabrafenib, included studies of immunotherapies, dacarbazine (DTIC) and trametinib. Company felt most relevant scenario was to include studies that had assessed technologies in

people who were treatment naïve and with the BRAF V600 mutation (did not include patients without this mutation).

- The company only presented results for an indirect comparison of cobimetinib + vemurafenib with dabrafenib.
  - PFS 0.599, 95% CI 0.47 to 0.86
  - OS 0.635, 95% CI 0.46 to 0.77

Figure 4. Network of evidence for OS and PFS in studies of people with BRAF V600 mutation positive melanoma (company submission figure 11 page 76)



TM2mg = trametinib 2mg; DTIC = dacarbazine, DB = dabrafenib, VM = vemurafenib, DB.TM2mg = dabrafenib + trametinib 2mg; DB.TM1mg = dabrafenib + trametinib 1mg; VM.Cobi = vemurafenib + cobimetinib

Table 5: summary of trials included in the company's NMA (ERG report table 5 page 36, adapted from company submission table 20)

Trial reference	Trial arm A	Trial arm B	Trial arm C
coBRIM	Vemurafenib + cobimetinib	Vemurafenib + placebo	
BRIM-3	Vemurafenib	Dacarbazine	
Flaherty 2012a	Trametinib 1mg + dabrafenib	Trametinib 2mg + dabrafenib	Dabrafenib
Flaherty 2012b	Trametinib 2mg	Chemotherapy (dacarbazine or paclitaxel)	
BREAK-3	Dabrafenib	Dacarbazine	
COMBI-d	Trametinib 2mg + dabrafenib	Dabrafenib	
Robert 2015a	Trametinib 2mg +	Vemurafenib	

(COMBI-v)	dabrafenib		

ERG comments

4.9 The ERG commented that:

- All relevant published evidence included.
- Network only includes only 1 trial for cobimetinib + vemurafenib and each comparator in the scope so the results should be considered with caution given the limited number of trials available.
- Company stated that some of the trials in the network may have had high risk of bias, but justification for this conclusion unclear. Most of the trials are large RCTs and the BREAK-3 and BRIM-3 trials informed NICE TA321 (for dabrafenib) and TA269 (for vemurafenib) respectively.
- Clinical heterogeneity of the trials and trial populations not fully explored but trials in the network are broadly similar based on selected patient characteristics presented.
- Patient crossover in BREAK-3 and BRIM-3 does not appear to be adjusted for, and may therefore underestimate the treatment effect of dabrafenib and vemurafenib respectively compared with darcarbazine.
- AFT modelling approach appropriate.

Adverse effects of treatment

4.10 Safety data are from the May 2014 analysis and included 493 patients who had received at least 1 dose of the study drug.

- Adverse effects (any grade) that were **more** common with cobimetinib + vemurafenib than vemurafenib were: diarrhoea, photosensitivity, nausea and vomiting, elevated creatine phosphokinase levels, serious retinopathy and raised liver enzyme levels. Grade 4 adverse events were more common with cobimetinib + vemurafenib (13%) than vemurafenib (9%) attributed mostly to grade 4 creatine phosphokinase levels in 4% of cobimetinib + vemurafenib and 0% vemurafenib arm.

- Adverse effects (any grade) that were **less** common with cobimetinib + vemurafenib than vemurafenib were: arthralgia, alopecia and cutaneous neoplasms (specifically secondary cutaneous squamous cell carcinoma and keratoacanthoma).
- The company stated that adverse events that are associated with MEK inhibitors (such as cobimetinib) and were observed in coBRIM were: elevated creatine kinase levels and retinopathy (serious retinopathy was observed in 26% in cobimetinib + vemurafenib are and 3% in the vemurafenib arm). The company stated that both of these adverse effects can be managed with treatment interruption, dose reduction or discontinuation. The company noted that the SmPC recommends that at each treatment visit, patients taking cobimetinib should be assessed for new or worsening visual disturbances.

Table 6: summary of adverse event data presented in pages 89 to 90 of company submission

	Cobimetinib+ vemurafenib	vemurafenib
Permanent discontinuation due to an adverse event	13%	12%
Serious adverse event	29.5%	25.1%
Deaths attributed to adverse events	6 (in 2 people the adverse event was recorded as the primary cause of death [cardiac arrest and pneumonia]; 2 people primary cause of death recorded as 'other' [unexplained, asthenia and fatigue];	3 (1 because of cardiac arrest, 2 because of disease progression)

	in 2 people death was because of disease progression)	
Deaths attributed to study treatment	1 (fatigue and asthenia)	1 (cardiac failure)

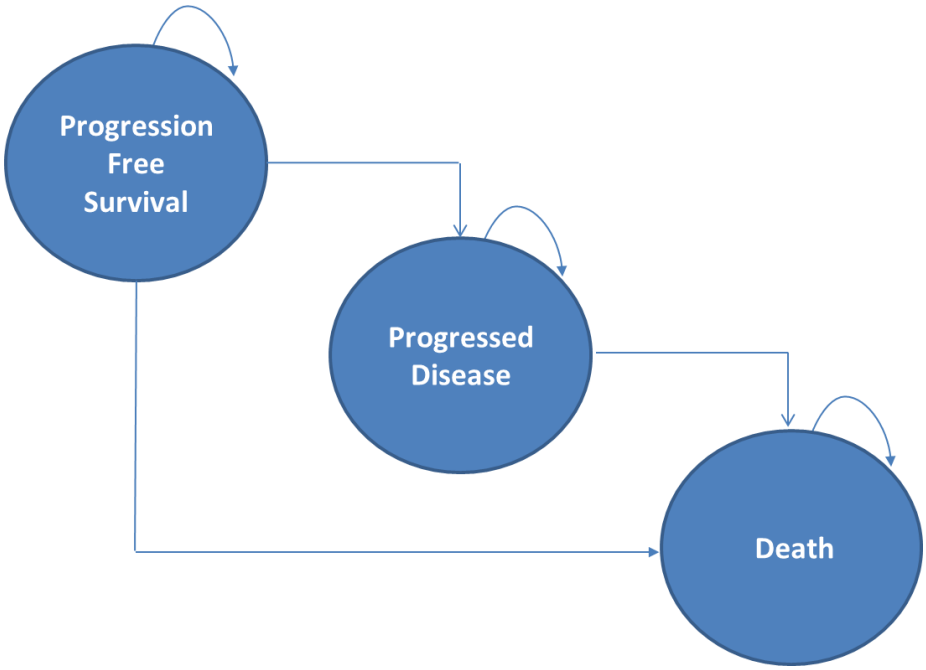
5 Cost-effectiveness evidence

Model structure

5.1 Three state partitioned survival model (company says this model is the same approach as used in TA269 and TA321).

- Time horizon 30 years
- Cycle length 7 days with half cycle correction
- 3.5% discount rate and from NHS/PSS perspective
- The modelled population is based on the trial population in coBRIM
- Once people have disease progression (or have unacceptable toxicity) they stop treatment and it is assumed they receive no further anti-cancer therapy (i.e. no adjustments were made in the survival modelling for subsequent treatments)

Figure 5: model structure, company submission figure 15 page 98



ERG comments on model structure

5.2 The ERG considered:

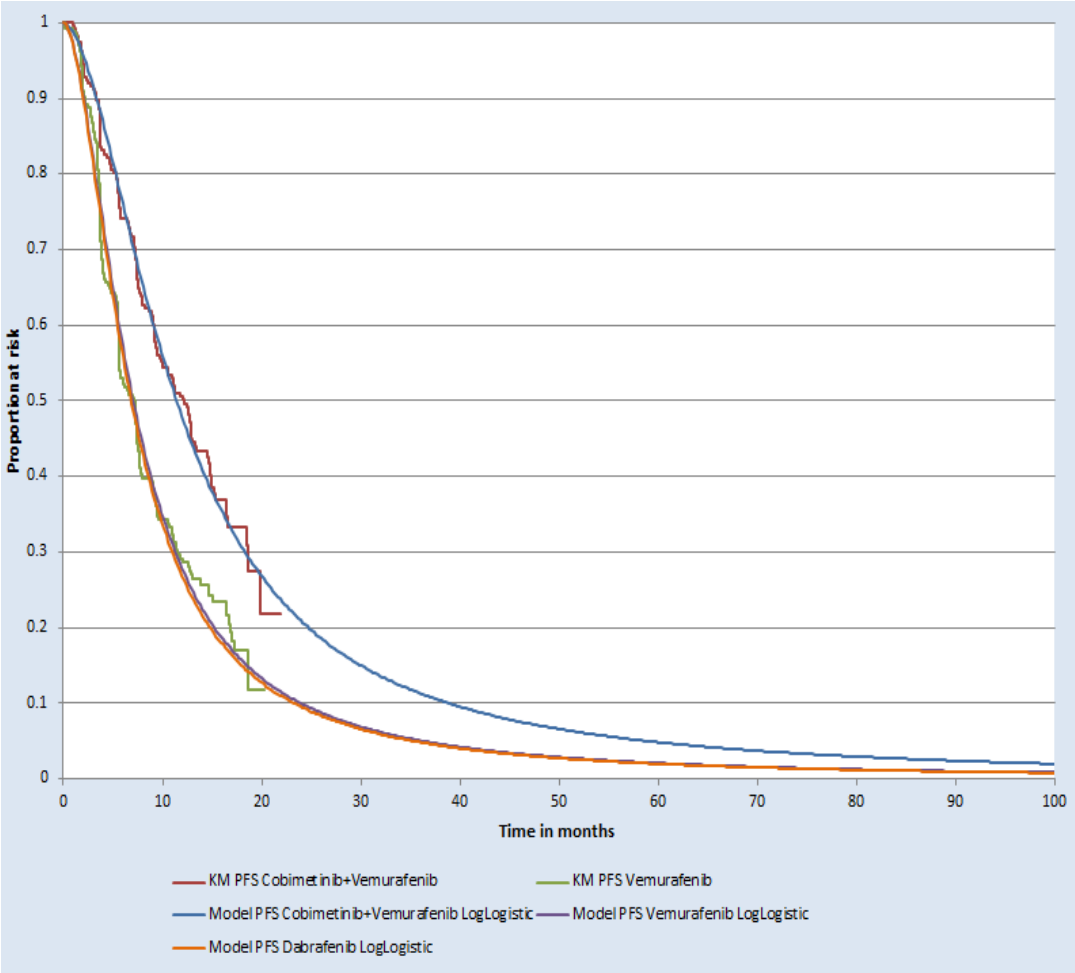
- Model structure, time horizon and modelled population appropriate.
- Reasonable not to model subsequent treatments after disease progression separately because the frequency and type of subsequent treatment was similar in both study arms in coBRIM and people spent a similar length of time with progressed disease in both arms.

Incorporation of progression free survival and overall survival data in model

5.3 Data for progression free survival for cobimetinib + vemurafenib and vemurafenib came from coBRIM. For its comparison of cobimetinib + vemurafenib with dabrafenib the company used its estimates from its indirect comparison. The trial data was extrapolated. The company checked for proportional hazards and tested the statistical fit of a number

of parametric distributions to the trial data (see table 29 in the company submission for all distributions tested). The company stated that the log-logistic distribution had the best statistical fit to the trial data for PFS.

Figure 6 extrapolated and Kaplan Meier estimates for PFS (company submission figure 16 page 103)



5.4 Survival data from coBRIM was also extrapolated and used in the model, but an adjustment was also made to account for the observation in clinical practice that the rate of death for people with stage IV metastatic melanoma considerably decreases if they have survived over 5 years after disease progression. Please see figures 18 and 19 in the company's submission to support applying this adjustment (these are Kaplan Meier estimates over 76 months from a study comparing ipilimumab with dacarbazine in metastatic melanoma and survival curves by melanoma disease stage from the SEER registry over 10 years). The method for this

adjustment was called ‘mixture cure-rate’. It involved estimating the proportion of people in the coBRIM (and therefore modelled population) who had the same probability of dying from cancer and dying from non-cancer causes at any point of time. These estimates were made using data from the SEER registry and background mortality rates (from the US). In the absence of patient level data on dabrafenib, the adjustment for background mortality rates were based on the coBRIM patient population. This was called the ‘cure rate fraction’ and was estimated at [redacted]. The extrapolation used a log-normal distribution and incorporated the cure rate fraction adjustment.

[redacted]

ERG comments on how progression free and overall survival data are used in model

5.5 The ERG considered:

- The choice of parametric distribution for extrapolating PFS (log-logistic) was reasonable. It noted that lognormal and gamma distributions also had a reasonable fit to the trial data and resulted in larger ICERs compared with vemurafenib, but overall the difference in QALYs of choosing different distributions was small.
- The company chose a [redacted] distribution to extrapolate survival data from coBRIM. The ERG noted that the ICER for cobimetinib + vemurafenib compared with vemurafenib was sensitive to the choice of parametric curve used for extrapolating overall survival.
- CoBRIM only had follow up for 18 months. 4 year follow up data for people treated with vemurafenib (Puzanov et al) showed a similar rate of survival to the company's overall survival with the adjustment for people who have stable progressed disease (figure 9 ERG report page 72) and this supported using the adjustment in the model.

Quality of life data used in the model

5.6 EQ-5D 5L data were collected in coBRIM, before starting any treatment, while patients had not progressed and for a small proportion of people after their disease had progressed (n=57). The company assumed that the utility values for dabrafenib would be the same as vemurafenib. The company estimated utility values from the EQ-5D-5L data using 2 validated approaches (crosswalk – a mapping method and by using the Office of Health Economics (OHE) scoring algorithm).

- **PFS health state**: The company noted that the OHE algorithm is usually preferred because it is specific to England, but noted that this method resulted in utility values that were higher than the population norms for the average age of patients in coBRIM, which it heard from

its clinical advisers was implausible. The company therefore used the crosswalk values in its base case for the PFS health state (a comparison of the crosswalk and OHE utility values are presented in table 33, page 115 of the company submission)

- **Progressed disease health state**: The company stated that in TA269 the Appraisal Committee and the ERG for that appraisal suggested that patients who remain in a progressed, but stable disease-state would be expected to experience an improved utility after 5 years of survival. The company noted that the progressed disease EQ-5D-5L data from coBRIM were from patients up to 12 weeks after they had stopped their study treatment, and were not representative of people with prolonged stable progressed disease. The company preferred to use utility values estimated in Beusterien et al (2009), which had been used in TA267 because Beusterien provided estimates for people with progressed disease (of less than 5 years duration) and people with stable prolonged progressed disease (of over 5 years duration). The company noted the utility values from Beusterien et al were not consistent with the NICE reference case because they were not elicited directly from patients (rather they were from the general public).

Table 7: summary of utility values used in the company base case (company submission table 36 page 121)

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
PFS (cobimetinib + vemurafenib)	0.837 (0.004)	0.830, 0.844	5.4.1	Derived from EQ-5D-5L results directly from the coBRIM study
PFS (vemurafenib)	0.819 (0.004)	0.812, 0.827	5.4.1	
PFS (dabrafenib)	0.819 (0.004)	0.812, 0.827	5.4.1	Consistent with vemurafenib monotherapy
PD <5 years	0.590 (0.02)	0.578, 0.602	5.4.4	Limited data available for health state from coBRIM study. UK standard gamble study assessing
PD ≥5 years	0.770 (0.02)	0.755, 0.785	5.4.4	

				melanoma health states

ERG comments on quality of life data used in the model

5.7 The ERG commented:

- For the HRQoL data from the trial (used for the PFS health state), it was not clear how observations from individual patient data were pooled to estimate health state weights for HRQoL. In particular whether results were properly adjusted for baseline utility in both arms of the trial or whether observations for some patients were missing, and if so, how missing data were handled.
- The impact of adverse events on quality of life was not modelled; rather the company assumed that the average utility for cobimetinib + vemurafenib compared with vemurafenib would incorporate the impact of any adverse events. Given the ERG's concerns about how missing HRQoL data was handled, there was uncertainty surrounding the quality of life difference between cobimetinib + vemurafenib and vemurafenib and the reasons for this difference.
- Using the crosswalk method to obtain equivalent 3L values for the EQ-5D-5L data collected in the coBRIM trial and testing OHE values in a scenario analysis was a reasonable approach.
- For the PD health state it is reasonable to assume a higher utility value for people with stable progressed disease (who have survived over 5 years with progressed disease) and this approach was used in TA269. However, the source of data (Beusterien et al 2009) did not meet the NICE reference case because the HRQoL data was not collected from patients.
- The ERG suggested an alternative utility value for the PD health state of 0.73, which had been used in TA384 and was derived from patients with advanced (unresectable or metastatic) melanoma who were participating in the CheckMate 066 trial of nivolumab (Robert et al 2015 -utility values for progressed disease were estimated as 0.7277 for

patients ≥ 30 days from death and 0.7054 for patients <30days from death in this publication).

Cost data used in the model

5.8 The list prices of cobimetinib, vemurafenib and dabrafenib are presented in table 3. The company adjusted the monthly costs for cobimetinib and vemurafenib for dose modifications in coBRIM. It assumed that all patients would receive 100% of the dabrafenib dose, as per the label dose. It was assumed that all treatments would be dispensed monthly and no adjustments were made for drug wastage The monthly (list price) costs in the model were therefore:

- cobimetinib + vemurafenib: £10,748.60
- vemurafenib: £6625.49
- dabrafenib: £6066.67

5.9 The company used 2 different approaches to model time on treatment in its comparison of cobimetinib + vemurafenib with vemurafenib and its comparison of cobimetinib + vemurafenib with dabrafenib

- **Cobimetinib + vemurafenib compared with vemurafenib**. The company extrapolated time on treatment from coBRIM data on when people stopped treatment (either because of unacceptable toxicity or disease progression). The Weibull distribution gave the best statistical fit for the cobimetinib + vemurafenib data and the log-logistic gave the best statistical fit to the vemurafenib data. The modelled mean and median times on treatment for cobimetinib + vemurafenib and vemurafenib are given in table 40 of the company submission page 126.
- **Cobimetinib + vemurafenib compared with dabrafenib.** The company used progression free survival as a proxy for time on treatment because it did not have data for time to treatment discontinuation for dabrafenib.

5.10 Health state costs were assumed to be £378 per month in both the PFS and progressed disease health states in the model. The costs of treating adverse events of grade 3 or 4, at an incidence of 3% or more were incorporated in the model. Because no data were available to the company for dabrafenib, it was assumed the resource costs associated with adverse events would be the same for dabrafenib as for cobimetinib + vemurafenib. Incorporating the adverse events and costs into the economic model, resulted in a weekly adverse event cost of £3.20 for cobimetinib + vemurafenib and £3.90 for vemurafenib. The company suggested that the higher costs associated with vemurafenib alone were driven by the greater incidence of squamous cell carcinoma of the skin, as compared with cobimetinib +vemurafenib. A breakdown of the adverse events and associated costs incorporated in the model are given in table 43 of the company submission page 130.

ERG comments on cost data used in model

5.11 The ERG commented on the different approaches used to estimate time on treatment for cobimetinib + vemurafenib and vemurafenib compared with dabrafenib. It noted that using this approach resulted in higher treatment costs for dabrafenib.

5.12 The ERG commented that different approaches were used to estimate the drug doses a person would receive in clinical practice (for cobimetinib + vemurafenib and vemurafenib these were based on the actual dosages received in coBRIM, whereas for dabrafenib these were the label dosages. The ERG considered that a consistent approach should have been used for all technologies.

5.13 The ERG considered that there should be a decreasing health state cost for long term stable progressed disease following discussion with its clinical expert advisers. It suggested the following costs for the progressed disease health state year 1 £87.23/ week; year 2-3 £20.25 per week and year 4-6 £12.17 per week. The ERG also thought that because

there were very few differences in the incidence of adverse events between treatment arms that the costs of adverse events should be the same. It tested both of these assumptions in scenario analyses.

Company's base-case results and sensitivity analysis

5.14 The company presented 2 pairwise comparisons (cobimetinib + vemurafenib compared with vemurafenib, cobimetinib + vemurafenib compared with dabrafenib) rather than a fully incremental analysis because of the difference in approach to modelling time on treatment for these 2 comparisons. The company presented results using list prices for cobimetinib, vemurafenib and dabrafenib. At the request of NICE the ERG presented the equivalent results including the confidential patient access schemes for vemurafenib and dabrafenib. All ICERs including the patient access scheme costs of vemurafenib and dabrafenib presented subsequently in this document are commercial in confidence, have been calculated by the ERG and are documented in the ERG's confidential appendix.

Table 8 Company base case results, for the pairwise comparison of cobimetinib + vemurafenib with vemurafenib using time on treatment from coBRIM (company submission table 46 page 138, table 57 page 147 and ERG confidential appendix table 1 page 2 [for with-PAS results])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Cobimetinib + vemurafenib	£163,974	4.015	3.034					
Vemurafenib monotherapy	£81,984	3.392	2.489	£81,990	0.622	0.545	£150,514	£150,514 (£151, 668 probabilistic) [redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 9 Company base case results for the pairwise comparison of cobimetinib + vemurafenib with dabrafenib using PFS as a proxy for time on treatment (company submission table 47 page 138, table 58 page 147 and ERG confidential appendix table 2 page 2 for with-PAS results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Cobimetinib + vemurafenib	£208,047	4.015	3.034					
Dabrafenib	£78,392	3.281	2.417	£129,655	0.733	0.618	£209,942	£209,942 (£215,264 probabilistic) [redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Company sensitivity analyses

5.15 The company carried out deterministic sensitivity analyses and presented the results for the cobimetinib + vemurafenib compared with vemurafenib comparison. The ICER was most sensitive to the: weekly cost of cobimetinib; weekly cost of vemurafenib (when in combination with cobimetinib); supportive costs for PFS; the utility value for people receiving cobimetinib + vemurafenib in the PFS health state; the utility value for people receiving vemurafenib in the PFS health state and utility values in the progressed disease health state (please see table 59 company submission page 151).

5.16 The company carried out a number of scenario analyses surrounding its assumptions on parametric distributions used to extrapolate overall and progression free survival data from the trials; utility values, dose and treatment durations (including presenting results when PFS was used to estimate time on treatment for both the comparison between cobimetinib + vemurafenib with vemurafenib and with dabrafenib [scenario 15]). The company also presented scenarios in which it changed the discount rate and time horizon. In all of these scenarios the ICER for either pairwise comparison remained over £130,000 per QALY gained. The company stated that it had not proposed a patient access scheme for cobimetinib because even setting the cost of cobimetinib to £0 resulted in ICERs over what NICE would consider within an acceptable range (see scenario 20).

Table 10 Company scenario analyses (company submission table 60 page 152, N.B. extra summary of base case for some scenarios added, with-PAS results calculated by ERG and reported in table 4 of the confidential appendix)

Scenario	Base case	Analyses	ICER intervention vs. vemurafenib	ICER intervention vs. dabrafenib
Base case	n/a	n/a	£150,514 [redacted]	£209,942 [redacted]
	OS parametric distribution			
1	Log-normal	Exponential	£161,902 [redacted]	£219,912 [redacted]
2		Weibull	£229,890 [redacted]	£269,146 [redacted]

3		Log-logisitic	£175,592 [redacted]	£212,255 [redacted]
4		Gompertz	£253,766 [redacted]	£269,898 [redacted]
5		Gamma	£217,135 [redacted]	£262,084 [redacted]
	PFS parametric distribution			
6	Log-logistic	Exponential	£166,292 [redacted]	£193,165 [redacted]
7		Weibull	£157,072 [redacted]	£169,530 [redacted]
8		Gamma	£164,485 [redacted]	£191,655 [redacted]
9		Log-normal	£157,377 [redacted]	£203,455 [redacted]
10		Gompertz	£152,215 [redacted]	£164,942 [redacted]
	Utilities			
11	Crosswalk approach for deriving utility values from coBRIM EQ-5D-5L data (PFS state)	Alternative health state utilities using the OHE value set for EQ-5D-5L valuation	£143,536 [redacted]	£200,778 [redacted]
12	2 utility values used in PD health state (PD before 5 years , stable PD after 5 years)	Alternative health states utilities using one value (0.59) for all PD	£157,952 [redacted]	£219,640 [redacted]
	Dose / treatment duration			
13	Weibull	KM with Exponential tail for cobimetinib and vemurafenib (when in combination), TOT	£137,839 [redacted]	£209,942 [redacted]
14	Log-logistic	KM with Log-normal tail for vemurafenib (when monotherapy), TOT	£159,817 [redacted]	£209,942 [redacted]
15	Time on treatment (TOT) from coBRIM (for cobimetinib + vemurafenib vs. vemurafenib)	PFS as a proxy for TOT for cobimetinib + vemurafenib vs. vemurafenib	£221,732 [redacted]	£209,942 [redacted]
16	Dosing as per coBRIM for cobimetinib + vemurafenib	Dosing as per label for cobimetinib + vemurafenib vs. vemurafenib	£170,305 [redacted]	£254,301 [redacted]

	vs. vemurafenib			
	Discount rate: effects and costs			
17	3.5%	1.5%	£140,198 [redacted]	£203,763 [redacted]
	Time horizon			
18	30	20	£152,911 [redacted]	£209,811 [redacted]
19		10	£169,632 [redacted]	£217,655 [redacted]
	Drug costs			
20		£0 cobimetinib	£53,358 [redacted]	£90,977 [redacted]

ERG exploratory analyses

5.17 The ERG noted that the company had made an error in its deterministic sensitivity analysis surrounding the weekly cost of vemurafenib because the cost for vemurafenib was only altered in the cobimetinib + vemurafenib arm and not the vemurafenib arm. The ERG repeated this sensitivity analysis changing the cost of vemurafenib in both arms resulting in the ICER for cobimetinib + vemurafenib compared with vemurafenib decreasing from £150,514 per QALY gained to £126,000 per QALY gained when the cost of vemurafenib was reduced by 50% and increasing to £174,916 per QALY gained when the cost of vemurafenib was increased by 50%.

5.18 The ERG carried out the sensitivity analyses presented in table 12

Table 11 ERG scenario analyses (table 30 page 95 ERG report, with explanation of the rationale for the scenarios added). The scenarios in bold text are included in the ERG's preferred base case (see section 5.19 of this pre-meeting briefing). The with-PAS results were calculated by the ERG and are reported in table 6 of the ERG's confidential appendix)

Comparator/scenario	**Base case**	**Value used in analysis**	**vs. vemurafenib ICER (£/QALY)**	**vs. dabrafenib ICER (£/QALY)**
Company base case results:	-	-	£150,514 [redacted]	£209,942 [redacted]
i) Cure rate fraction removed (because company had not tested this in its own sensitivity analyses)	[redacted]	0	£137,928 [redacted]	£190,964 [redacted]
ii) TOT extrapolation curve changed for vemurafenib + cobimetinib (so that both cobimetinib + vemurafenib and vemurafenib data extrapolated using same parametric distribution for extrapolation)	**KM with Weibull tail**	**KM with log-logistic tail**	**£204,340** [redacted]	**£209,942** [redacted]
iii) Utility values **PFS vemurafenib + cobimetinib (so that the utility value the cobimetinib + vemurafenib, vemurafenib and dabrafenib arms are the same for the PFS health state**	**0.837**	**0.819**	**£158,414** [redacted]	**£219,603** [redacted]
iii) Utility values **PD (changed so that the same utility value is used as TA384 for this health state)**	**0.59; 0.77**	**0.73**	**£154,717** [redacted]	**£211,447** [redacted]

iv) Dabrafenib dose (reduced label dosage to the same extent as seen in the cobimetinib + vemurafenib arm of coBRIM [by 12%])	**£1400 per week**	**£1232 per week**	**£150,514** [redacted]	**£223,277** [redacted]
v) Shorter treatment duration (patients could be treated for a shorter duration than in the MA i.e. could stop treatment before disease progression) N.B. clinical advise to the ERG was that people would be unlikely to stop treatment before disease progression if they have acceptable toxicity	Treat until disease progression	Treat for a maximum 2 years	£123,478 [redacted]	£139,532 [redacted]
vi) Subsequent treatment costs included	No subsequent treatment	Subsequent treatment £1400 / week	£149,669 [redacted]	£219,201 [redacted]
vii) Dabrafenib OS (assumed to be the same as vemurafenib because the effectiveness of dabrafenib may have been underestimated in the company's NMA because crossover in the dabrafenib trial did not appear to be adjusted for)	0.635	0.7	£150,514 [redacted]	£243,836 [redacted]
viii) Combination analysis (scenarios ii, iii & iv)[a]	**See scenarios above**	**See scenarios above**	**£210,046** [redacted]	**£224,877** [redacted]

[a] The combination analysis includes changes for scenario iii only for PD utilities and not for PFS utilities.

ERG's exploratory base case

5.19 The ERG presented an exploratory base case with a fully incremental analysis comparing cobimetinib + vemurafenib with vemurafenib and dabrafenib. In order to do this the ERG used:

- PFS and OS estimates for cobimetinib + vemurafenib and vemurafenib from the network meta-analysis rather than using the coBRIM trial data directly in the model.
- PFS as a proxy for time on treatment for all treatment arms. The ERG estimated that using PFS as a proxy rather than trial data overestimated drug costs, drug administration and adverse event costs by approximately 7%. The ERG therefore reduced these costs by 7% (multiplied by 0.93 in the model) in its exploratory base case. The extrapolation of data used the same parametric distribution in each treatment arm (see ERG scenario ii).
- All drug costs were reduced by 12% to account for a proportion of people using a lower dosage than stated in the marketing authorisations for all modelled treatments (see ERG scenario iv).
- Quality of life estimates taken from the coBRIM trial for PFS and from the nivolumab NICE TA384 for progressed disease (see ERG scenario iii).

Table 12 ERG's exploratory base case (table 32 page 101 ERG report). The with-PAS results were calculated by the ERG and are reported in table 7 of the ERG's confidential appendix)

	QALY	Cost	Incremental QALY	Incremental Cost	ICER (£/QALY)
Dabrafenib	2.479	£65,908 [redacted]			[redacted]
Vemurafenib	2.576	£77,846 [redacted]	0.10	£11,938	£123,072 [redacted]
Vemurafenib + cobimetinib	3.092	£193,295 [redacted]	0.52	£115,449	£223,738 [redacted]

Innovation

5.20 Justifications for considering cobimetinib to be innovative:

- Company:
  - Offers additional mechanism of action to vemurafenib by inhibiting MEK, enhancing the action of vemurafenib which targets the same signalling pathway. Reduces the possibility of drug resistance to monotherapy. Company considers this a step-change in the management of the condition.
  - The relatively young average age of patients with metastatic melanoma means they are likely to be of working age. The personal and wider societal benefit derived through prolonging patients survival and slowing disease progression is not currently captured in the QALY calculation
  - Cobimetinib is an oral treatment allowing patient choice and flexibility in administration
- ERG:
  - The company's suggested reasons for cobimetinib being innovative apply to patients in whom BRAF inhibitor therapy is considered to be the most appropriate first line treatment for advanced disease.
  - Dabrafenib is also an oral treatment. Ipilimumab, pembrolizumab and nivolumab are administered intravenously.

6 End-of-life considerations

Table 13 End-of-life considerations

Criterion	Data available

The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Company: "patients with advanced melanoma have a 1- year survival rate of 25% and a median overall survival of ~6 months (Jarkowski, Norris and Trinh 2014)" coBRIM median overall survival vemurafenib 17.4 months model median overall survival vemurafenib17.0 months The ERG did not comment specifically on this criterion but overall agreed with the company that all end of life criteria had been met for cobimetinib (NB ID661 FAD section 4.15 "the committee recognised that median overall survival in the monotherapy groups of the trials was less than 24 months, but that the modelled mean survival was more than 24 months. The committee appreciated that the difference in median and mean survival estimates may reflect the small number of people who survive many years with this condition, and did so even before effective treatments were available as demonstrated in the AJCC registry. It considered that as treatment for advanced melanoma improves, overall survival is likely to increase to more than 24 months [but currently this criterion is met]")
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	CoBRIM difference in median survival cobimetinib +vemurafenib and vemurafenib = 4.9 months (22.3-17.4 months) Model difference in median survival cobimetinib + vemurafenib and vemurafenib = 6.9 months (23.9 – 17.0) (company table 48 page 140) submission The incremental life year gain in the model was 0.622 for cobimetinib + vemurafenib compared with vemurafenib and 0.733 for cobimetinib + vemurafenib compared with dabrafenib The ERG commented that it considered data from coBRIM supported this criterion being met
The treatment is licensed or otherwise indicated for small patient	Company: • 10,650 patients in England in Wales have

populations. NB since April 2016 it was agreed by the NICE Board as part of the Cancer Drugs Fund process and methods update that this criterion no longer needs to be met for end of life considerations.	malignant melanoma • 2,343 (22%) advanced melanoma • Of these 797 (34%) have BRAF V600 mutation • Assumed 12% will enter clinical trials • Overall 576 people will be eligible for cobimetinib + vemurafenib in England and Wales ERG commented that the rate of cutaneous mutations with the BRAF V600 mutation may be around 50% rather than 34% (NB ID661 FAD section 4.15 states: "[the committee] accepted that the patient population for unresectable or metastatic BRAFV600 mutation-positive melanoma is small (approximately 1,000 patients annually)"

7 Equality issues

7.1 No equalities issues were raised by the company, ERG or consultees or during the scoping process for this appraisal.

8 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

The link to the European public assessment report for cobimetinib is here:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003960/WC500198565.pdf

The link to the summary of product characteristics for cobimetinib is here:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003960/WC500198563.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma

Final Scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of cobimetinib in combination with vemurafenib within its marketing authorisation for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma.

Background

Melanoma is a cancer of the skin. In its early stages, melanoma is normally asymptomatic and can often be cured by surgery (resection). However, it can spread or metastasise to nearby lymph nodes (stage III) or to other parts of the body (stage IV). Most melanomas occur in people with pale skin. The risk factors are skin that tends to burn in the sun, having many moles, intermittent sun exposure and sunburn.

There were 11,281 new diagnoses of melanoma[1] and 1781 deaths registered in England in 2012.[2] In the UK, about 27% of people diagnosed with melanoma are younger than 50 years.[3] At diagnosis, around 1% of melanomas are stage IV.[3]

A mutated form of the BRAF gene (called BRAF V600) is found in about 50% of melanomas. The mutated gene means that the cells produce too much BRAF protein, leading to uncontrolled cell division and growth of the tumour.

Treatment options for advanced (unresectable or metastatic) melanoma depend on the person's BRAF mutation status and their treatment history. NICE technology appraisals (TA) guidance 269 and 321 recommend the BRAF inhibitors vemurafenib or dabrafenib respectively as options for treating BRAF V600 mutation-positive unresectable or metastatic melanoma. NICE TA guidance 319 and 268 recommend ipilimumab, which is not a BRAF-targeted therapy, for untreated or previously treated advanced (unresectable or metastatic) melanoma. In clinical practice, for people with BRAF mutation-positive advanced melanoma, a BRAF inhibitor is the usual first-line treatment; ipilimumab may be considered for first-line use in a subgroup of patients who are relatively well and in whom the disease is not progressing rapidly.

The technology

Cobimetinib (brand unknown, Roche Products) inhibits the action of the abnormal BRAF protein, with the aim of slowing the growth and spread of the cancer. Cobimetinib is administered orally.

Cobimetinib in combination with vemurafenib does not currently have a marketing authorisation in the UK for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. It has been studied in a clinical trial in combination with vemurafenib, compared with vemurafenib alone in adults with unresectable stage IIIc or stage IV metastatic melanoma who had not received any previous treatment.

Intervention(s)	Cobimetinib in combination with vemurafenib
Population	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma
Comparators	• dabrafenib • vemurafenib
Outcomes	The outcome measures to be considered include: • progression free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life
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 comparator technologies will be taken into account.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Dabrafenib for treating unresectable or metastatic BRAFV600 mutation-positive melanoma (2014). NICE Technology Appraisal 321. Review date October 2017. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (2014). NICE Technology Appraisal 319. Review date June 2017. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (2012). NICE Technology Appraisal 268. Moved to static list, April 2015. Vemurafenib for the treatment of unresectable locally advanced or metastatic BRAFV600 mutation positive malignant melanoma (2012). NICE Technology Appraisal 269. Moved to static list, January 2015. Appraisals in development Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab. NICE technology appraisals guidance [ID760]. Publication expected December 2015. Pembrolizumab for treating ipilimumab naive unresectable, metastatic melanoma. NICE technology appraisals guidance [ID801]. Publication expected January 2016. Nivolumab for treating advanced, unresectable or metastatic melanoma. NICE technology appraisals guidance [ID845]. Publication expected May 2016. Talimogene laherparepvec for treating metastatic melanoma. NICE technology appraisals guidance [ID508]. Publication expected July 2016. Tramatenib with dabrafenib for treating advanced, unresectable or metastatic BRAF V600 mutation-positive melanoma. NICE technology appraisals guidance [ID815]. Publication expected August 2016. Related Guidelines: Melanoma: assessment and management of melanoma

	(2015). NICE guideline 14. Review date to be confirmed. Related Quality Standard: In development: skin cancer. NICE quality standard. Publication expected August 2016. Related NICE Pathway: Skin cancer (updated February 2015) NICE pathway. http://pathways.nice.org.uk/pathways/skin-cancer Other guidance: Cancer Service Guidance, May 2010, 'Improving outcomes for people with skin tumours including melanoma'.
Related National Policy	Department of Health, 2011, Improving outcomes: a strategy for cancer. Department of Health, 2009, Cancer commissioning guidance. NHS England Manual for Prescribed Specialised Services 2013/14. Chapter 105. Specialist cancer services (adults) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1–5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

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Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Roche Products (cobimetinib) Patient/carer groups • Afiya Trust • Black Health Agency • British Skin Foundation • Cancer 52 • Cancer Black Care • Cancer Equality • Equalities National Council • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients' Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Melanoma UK • Muslim Council of Britain • OcuMel UK • Rarer Cancers Foundation • Skcin - Karen Clifford Skin Cancer Charity • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Professional groups • Association of Cancer Physicians • British Association of Dermatologists • British Association of Skin Cancer Specialist Nurses • British Dermatological Nursing Group • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Skin Foundation • Cancer Research UK • Melanoma Focus • Primary Care Dermatology Society	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Novartis (dabrafenib) • Roche Products (vemurafenib) Relevant research groups • British Society for Dermatological Surgery • Cochrane Skin Group • Institute of Cancer Research • MRC Clinical Trials Unit • Myfanwy Townsend Melanoma Research Fund • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Skin Cancer Research Fund • Skin Research Centre • Skin Treatment & Research Trust Evidence Review Group • Liverpool Reviews & Implementation Group, University of Liverpool

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS North, East, West Devon CCG • NHS North & West Reading CCG • Welsh Government	• National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Collaborating Centre for Cancer <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

Company evidence submission

February 2016

File name	Version	Contains confidential information	Date
Cobimetinib metastatic melanoma evidence submission (ID815)	**Final**	**Yes**	**5th February 2016**

Contents

Tables and figures

Abbreviations

AE	Adverse Event
AIC	Akaike information criterion
BIC	Bayesian information criterion
BORR	Best overall response rate
BSC	Best Supportive Care
CEAC	Cost Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CR	Complete Response
CRUK	Cancer Research UK
CSR	Clinical Study Report
cuSCC	cutaneous Squamous-Cell Carcinoma
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMYY	Embase
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research & Cancer Quality of Life Questionnaire
EQ-5D-3L	EuroQOL 5-Dimension-3 level
EQ-5D-5L	EuroQOL 5-Dimension-5 level
FAS	Full Analysis Set
FPFV	First-patient first-visit
HR	Hazard Ratio
HRQoL	Health related quality of life
HSUV	Health state utility values
ICER	Incremental Cost Effectiveness Ratio

ITT	Intention to Treat
KA	Keratoacanthomas
KM	Kaplan-Meier
MDD	Minimal Detectable Difference
NDA	New drug application
OS	Overall Survival
ORR	Overall response rate
PD	Progressed Disease
PFS	Progression Free Survival
PR	Partial Response
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RR	Response Rate
SD	Stable Disease
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMR	Society for Melanoma Research
SR	Serious retinopathy
TA	Technology Appraisal

1. Executive summary

BRAF V600 Mutation Positive Advanced Melanoma

Malignant melanoma is a tumour which arises from melanocytic cells and primarily involves the skin. Tumours may arise de novo or from pre-existing skin naevi (moles).

In 2011, there were 11,121 new cases of malignant melanoma in England. In the UK, about 27% of people diagnosed with melanoma are younger than 50 years (CRUK,[b]). Approximately 90% of melanomas are diagnosed as primary tumours without any evidence of metastasis and can often be definitively treated with surgery alone (resection) (CRUK,[a]).

However, for patients whose melanoma has metastasised (Stage IV), or is unresectable (Stage IIIb), prognosis is extremely poor. Until recently the median overall survival with stage IV melanoma was around 6 months, and approximately 80% of patients diagnosed with advanced melanoma will have died less than 2 years after diagnosis (Xing 2010). The standard systemic therapy was single-agent dacarbazine (DTIC) a cytotoxic drug which produced low response rates and for which there was no evidence of survival benefit.

In recent years there has been real progress in improving outcomes for patients with unresectable melanoma built of a greater understanding of the biology and pathology of the disease, including the role of the BRAF gene mutation. The BRAF gene mutation drives abnormal cell growth and provides a rational target for drug therapy; along with downstream molecules in the same cell signalling pathway, such as mitogen-activated protein kinase kinase (MEK). Of patients with stage IV melanoma, around 40% will have a mutated BRAF V600 gene (Lee, 2011). Because of its importance in driving treatment choice, BRAF mutation testing is part of the standard diagnostic work up for patients with melanoma in the UK. Taking into account a proportion of patients entering clinical trials, it is estimated that there are around 576 patients a year in England and Wales requiring treatment for BRAF mutated inoperable melanoma.

Current UK Clinical Practice

The treatment for this group of patients has been transformed in the last few years with the introduction of the selective inhibitors of mutated BRAF. NICE technology appraisal (TA) guidance 269 and 321 recommend the BRAF inhibitors vemurafenib or dabrafenib, respectively, as options for treating BRAF V600 mutation-positive unresectable or metastatic melanoma, and they have become the standard first-line treatment for most patients with BRAF mutant melanoma.

BRAF inhibitors are not the only effective new melanoma treatments introduced in recent years. NICE TA guidance 319 and 268 recommended ipilimumab, an immunotherapy whose activity is not dependent on BRAF mutation status, for untreated or previously treated advanced (unresectable or metastatic) melanoma. Recently, pembrolizumab has been appraised by NICE, and been recommended for use in patients who have progressed on prior ipilimumab (TA357) or without prior ipilimumab (TA366). A final appraisal determination (FAD) for nivolumab for treating advanced (unresectable or metatstatic) melanoma was published in January 2016 and is currently subject to appeal.

This is a rapidly evolving area of clinical practice, but for people with BRAF mutation-positive advanced melanoma, a BRAF inhibitor remains the usual first-line treatment. Ipilimumab or pembrolizumab may be considered for first-line use in a subgroup of patients who are relatively well and in whom the disease is not progressing rapidly. However, for BRAF mutation-positive patients, BRAF inhibitors are favoured because of their very high tumour response rates which are associated with rapid symptomatic relief, and generally good tolerability. Despite the recent updates to NICE technology appraisal guidance, it is anticipated that targeted therapies will remain the treatment of choice for patients with a BRAF mutation.

During the scoping phase for this appraisal, based on input from clinical experts and other stakeholders, it was agreed that ipilimumab, and other immunotherapies are not relevant comparators for cobimetinib + vermurafenib treatment.

Unmet need

Despite these developments there is still a need for improved treatments for BRAF mutated melanoma. Progression, following a period of tumour response, is common

with BRAF inhibition monotherapy and therapies which further delay progression are required to improve outcomes for patients with stage IV melanoma. Addition of the MEK inhibitor, cobimetinib (Cotellic), to vemurafenib was designed to do this by blocking the same signalling pathway at a downstream point, providing more complete blockade of aberrant cell signalling and interfering with one possible resistance mechanism.

Cobimetinib

Cobimetinib is administered in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. Cobimetinib is a highly selective oral inhibitor targeting the MEK enzyme in the mitogen-activated protein kinase (MAPK) pathway. Given with the BRAF inhibitor, vemurafenib, the combination simultaneously targets mutated BRAF V600 proteins and MEK proteins in melanoma cells, resulting in stronger inhibition of intracellular signaling, decreased tumour cell proliferation and overcoming mechanisms of resistance to BRAF inhibition by vemurafenib.

Cobimetinib is given at a dose of 60 mg, taken daily on days 1 to 21; followed by a 7 day break (Days 22 to 28). Vemurafenib is given at a dose of 960 mg twice a day (days 1-28 of each cycle). For each therapy there is the possibility of down-dosing as deemed clinically appropriate in response to toxicity. Both therapies are continued until disease progression.

Efficacy of cobimetinib

Cobimetinib, in combination with vemurafenib, has been studied in one phase III RCT (coBRIM) (Larkin, 2014) and one phase 1b dose finding study (BRIM7) (Ribas, 2014).

In coBRIM, vemurafenib + cobimetinib was compared to vemurafenib alone in treatment naïve patients with BRAF V600 mutation-positive unresectable locally advanced (Stage IIIc) or metastatic melanoma (Stage IV) (n=495). CoBRIM opened for recruitment in January 2013. Three efficacy analyses of the study have been conducted; the primary analysis in May 2014, an exploratory analysis requested by the EU assessors in January 2015, and the final overall survival (OS) analysis in August 2015.

The primary analysis was conducted with a clinical data cutoff of 9 May 2014. The study met its primary endpoint, with a statistically significant difference in progression free survival (PFS): 9.9 months in the intervention group, vs. 6.2 months in the comparator group (hazard ratio [HR] for death or disease progression 0.51, 95% confidence interval [CI], 0.39, 0.68, p<0.001).

The January 2015 analysis (one year after enrollment of the last patient) demonstrated a PFS of 12.3 months in the intervention group and 7.2 months in the control group (HR for death or disease progression, 0.58; 95% CI, 0.46 to 0.728) and an objective response rate (ORR) of 69.6% in the intervention group and 50% in the control group.

The final OS analysis (August 2015) demonstrated that median OS was 4.9 months longer in the intervention group, as compared to the control group (22.3 months vs. 17.4 months). The HR of 0.702 was statistically significant (p=0.005, 95% CI, 0.548-0.899). At this data cutoff one year survival rates were 75% and 64% for cobimetinib + vemurafenib and vemurafenib respectively. Two year survival rates were 48% and 38% for the treatment groups respectively.

The development of BRAF inhibitors transformed the treatment of metastatic melanoma. The efficacy results seen with the combination of cobimetinib + vemurafenib are a further step change in the management of this disease.

The anticipated role of cobimetinib in English clinical practice

For patients with BRAF mutation-positive advanced melanoma, treatment with BRAF inhibition is the usual first-line option. Vemurafenib monotherapy is approved by NICE, and used in this patient population (TA269, 2012). Statistically superior efficacy is achieved by treating patients with cobimetinib in combination with vemurafenib, as compared to vemurafenib monotherapy. BRAF inhibitor-mediated toxicity, in the form of development of new primary cutaneous malignancies, is seen at a lower frequency with the combination of cobimetinib + vemurafenib compared to vemurafenib alone. These effects are due to MEK inhibition blocking the paradoxical activation of the MAPK pathway induced by single-agent BRAF inhibitors. The MEK inhibitor-related adverse effects of cobimetinib are, generally, modest. As such,

treatment with cobimetinib in combination with vemurafenib is anticipated to replace treatment with monotherapy BRAF inhibitors, vemurafenib or dabrafenib.

Cobimetinib in combination with vemurafenib was granted European marketing authorisation on 20th November 2015.

Indirect treatment comparison vs. dabrafenib

As there is no head-to-head comparison between cobimetinib + vemurafenib to dabrafenib, a network meta-analysis (NMA) was conducted to allow an indirect treatment comparison (ITC). The accelerated failure time (AFT) model was determined to fit the data most appropriately, with PFS and OS as the outcomes of interest. The results of the analysis demonstrated cobimetinib + vemurafenib is more effective as compared to dabrafenib monotherapy treatment, for both PFS and OS outcomes. Inverse AFT results for cobimetinib + vemurafenib vs. dabrafenib were 0.599 (95% CI 0.47, 0.86) for PFS, and 0.635 (95%CI 0.46, 0.77) for OS.

Cost-effectiveness

A cost-utility analysis was conducted to evaluate the cost-effectiveness of cobimetinib + vemurafenib. The time horizon considered for the analysis is 30 years. This is deemed equivalent to a life-time horizon for this patient population, based on their poor prognosis and starting age. A three-state partitioned survival model (Progression Free Survival, Progressed Disease and Death) has been developed to model outcomes to this time point, based on the approach used in similar appraisals (TA269, 2012; TA321, 2014). The model takes the perspective of NHS England, and is consistent with the NICE reference case and the final scope of the appraisal.

The key model efficacy inputs are taken from the coBRIM study (Larkin, 2014), using the most recent data cuts for PFS (January 2015) and OS (August 2015). EQ-5D-5L data were collected from patients taking part in the coBRIM study, making it possible to elicit utility values directly from patients receiving cobimetinib + vemurafenib. Clinical trial results were extrapolated to the lifetime horizon, with sensitivity analysis to assess the impact of alternative approaches on base-case results.

The base case analysis estimated incremental costs of cobimetinib + vemurafenib vs. vemurafenib of £81,990 and £129,655 vs. dabrafenib (at list prices).

Combination treatment was associated with a total life-year and quality-adjusted life year (QALY) gain of 4.015 and 3.034, respectively. This leads to an incremental cost-effectiveness ratio (ICER) of £150,514 vs. vemurafenib and £209,942 vs. dabrafenib per QALY gained (at list prices).

In the scenario where the cost of cobimetinib is set to zero, the additional cost of vemurafenib (through extension of PFS provided by the addition of cobimetinib) leads to an ICER which exceeds the standard cost-effectiveness thresholds: cost-effectiveness may only be demonstrated if the manufacturer provides an additional subsidy to the NHS.

The limitations of standard HTA methodology when assessing combination treatments in metastatic disease are well recognised, and perverse outcome is ultimately to the detriment of groups of patients who remain in clear and recognised need of new therapies: reliance on cost-effectiveness analysis means these treatments cannot be approved for use in the NHS.

Should an immediate solution to this methodological issue not be found, the Committee must take these circumstances into account when coming to a recommendation in this appraisal.

Expert advisory panel

An expert advisory board was convened to provide feedback on the model structure, OS extrapolation methodology, resource use and utility inputs. The panel consisted of clinicians experienced in the management of patients with advanced melanoma, and health economists. At the one-day meeting, invited experts were briefed on the economic model structure and sources of key data inputs; their comments were recorded and taken into account in the subsequent development of the model.

1.1 Statement of decision problem

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma	
Intervention	Cobimetinib in combination with vemurafenib	Cobimetinib in combination with vemurafenib	
Comparator (s)	Vemurafenib monotherapy Dabrafenib monotherapy	Vemurafenib monotherapy Dabrafenib monotherapy	
Outcomes	progression free survival overall survival response rate adverse effects of treatment health-related quality of life	progression free survival overall survival response rate adverse effects of treatment health-related quality of life	
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	As per reference case	

	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 comparator technologies will be taken into account.		
Subgroups to be considered	Only patients with BRAF V600 mutation-positive melanoma will be considered	Only patients with BRAF V600 mutation-positive melanoma will be considered	
Special considerations including issues related to equity or equality	None highlighted	None highlighted	

1.2 Description of the technology being appraised

Table 2 Technology being appraised

UK approved name and brand name	Cobimetinib (brand name: Cotellic)
Marketing authorisation/CE mark status	Marketing Authorisation received 20th November 2015
Indications and any restriction(s) as described in the summary of product characteristics	Cobimetinib is indicated for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation
Method of administration and dosage	Oral 20mg tablet Treatment in combination with vemurafenib in patients with BRAFV600 mutation-positive melanoma tumour status. Recommended dose of cobimetinib is 60 mg (3 tablets of 20 mg) once daily. Cobimetinib is taken on a 28 day cycle. Each cobimetinib dose consists of three 20 mg tablets (60 mg) and should be taken once daily for 21 consecutive days (Days 1 to 21-treatment period); followed by a 7-day break (Days 22 to 28 - treatment break). Each subsequent cobimetinib treatment cycle should start after the 7-day treatment break has elapsed.

1.3 Summary of the clinical effectiveness analysis

Evidence for the clinical effectiveness and adverse reactions associated with the use of cobimetinib, in combination with vemurafenib, has been demonstrated in one phase III randomised controlled trial (RCT) (coBRIM) (Larkin, 2014).

CoBRIM is a multicentre, randomised, double-blind, placebo-controlled, Phase III study comparing vemurafenib + cobimetinib to vemurafenib alone in treatment naïve patients with BRAF V600 mutation-positive unresectable locally advanced (Stage IIIc) or metastatic melanoma (Stage IV) (n=495). The primary efficacy analysis was conducted in May 2014 with an exploratory analysis requested by the EU assessors in January 2015, and final OS analysis in August 2015.

The analysis conducted January 2015, (one year after enrollment of the last patient) demonstrated PFS of 12.3 months in the intervention group and 7.2 months in the control group, (HR for death or disease progression, 0.58; 95% CI, 0.46 to 0.728) and an ORR of 69.6% in the intervention group vs 50% in the control group. At this data cut, median OS had not been reached and the HR was not mature enough to convey significance. The final OS analysis was conducted on the dataset available at the August 2015 cut off. Median OS was 4.9 months longer in the intervention group, as compared to the control group (22.3 months vs. 17.4 months). The HR of 0.702 was statistically significant (p=0.005, 95% CI, 0.548-0.899). At this data cutoff, one year survival rates were 75% and 64% for cobimetinib + vemurafenib and vemurafenib respectively. Two year survival rates were 48% and 38% for the treatment groups respectively.

An ITC was required for comparison of cobimetinib + vemurafenib to dabrafenib. An NMA was developed with the AFT model determined to fit the data most appropriately. PFS and OS were the outcomes of interest. The results of the analysis demonstrated cobimetinib + vemurafenib is more effective as compared to dabrafenib monotherapy treatment, for PFS and OS outcomes. Inverse AFT results for cobimetinib + vemurafenib vs. .dabrafenib were 0.599 (95% CI 0.47, 0.86) for PFS, and 0.635 (95%CI 0.46, 0.77) for OS.

Strengths

The coBRIM study is a robust, high quality, adequately powered, centrally randomised trial which compared the intervention directly with the current standard treatment in UK clinical practice. The study was developed with the aid of investigator feedback, early phase studies, and published data. The study was conducted in 133 centres in 19 countries with a total of 495 patients randomised to cobimetinib + vemurafenib (n=247) or vemurafenib alone (n=248).

The coBRIM study demonstrated consistency between primary and secondary end points, and subgroup analysis, with the performance of the control group broadly consistent to prior randomised trials of BRAF inhibitors with regard to response rate and median PFS (Chapman 2011).

Limitations

Whilst not a limitation of the coBRIM study design, clinical evidence is not directly available for the Technology vs. the comparator dabrafenib. As such an indirect treatment comparison has been performed.

1.4 Summary of the cost-effectiveness analysis

The cost-effectiveness analysis was implemented in line with the appraisal scope, and reference case. A de novo model was developed to evaluate the cost effectiveness of cobimetinib + vemurafenib compared to either vemurafenib alone or dabrafenib alone. The three-state partitioned survival model was consistent with prior melanoma and oncology appraisals, and included the health states progression-free survival, progressed disease and death. These health states are appropriate to the patient clinical pathway, and to the clinical evidence available from the coBRIM study, and other melanoma studies.

The model projected health outcomes, to determine the QALY gain patients are expected to achieve when receiving cobimetinib + vemurafenib. EQ-5D-5L results were collected during the coBRIM study, thus allowing utilities to be derived directly from patients having received the intervention.

The model resulted in a total QALY gain of 3.034 and a life year gain of 4.015 for patients receiving cobimetinib + vemurafenib; an increase of 0.545 QALYs compared

to vemurafenib and 0.618 QALYs compared to dabrafenib. Results showed a gain of 0.622 and 0.733 life years as compared to vemurafenib and dabrafenib respectively. These results are in line with the observed evidence available for the coBRIM study, and highlight the clinical benefit patients with metastatic melanoma experience when receiving cobimetinib + vemurafenib.

Taking into account actual time on treatment from the coBRIM study, and assessing at published list prices, treatment with combination therapy lead to estimated lifetime costs of £163,974, compared to £81,984 for vemurafenib (Table 3). For the indirect comparison to dabrafenib, PFS was used as a proxy for time on treatment for both the intervention and comparator, resulting in total costs of £208,047 for combination therapy and £78,392 for dabrafenib monotherapy (Table 4). The resulting base-case ICERs vs. vemurafenib and dabrafenib monotherapy were £150,514 and £209,942 per QALY gained. In the scenario where the cost of cobimetinib is set to zero, the additional cost of vemurafenib (through extension of PFS provided by the addition of cobimetinib) leads to an ICER which exceeds the standard cost-effectiveness thresholds: cost-effectiveness may only be demonstrated if the manufacturer provides an additional subsidy to the NHS. This scenario is clearly unsustainable for the manufacturer and not supportive of expanding patient access to innovative technologies

The limitations of standard HTA methodology when assessing combination treatments in metastatic disease are well recognised (Session IP19 ISPOR European congress 2015; Pertuzumab NICE Appraisal ID523), with a NICE Decision Support Unit (DSU) Technical Support Document (TSD) unable to offer a solution (Davis S 2014) Indeed, the appraisal of the first submission to encounter this issue – pertuzumab (in combination with trastuzumab) in metastatic breast cancer – is still on-going, despite evidence submissions being made in April 2013.

This perverse outcome of the methodology is ultimately to the detriment of groups of patients who remain in clear and recognised need of new therapies: the EMA's assessment of clinical effectiveness supports licensing, but reliance on cost-effectiveness analysis means that they cannot be approved for use in the NHS. The

need for immediate collaboration between industry, NICE and the Department of Health to find a solution to this situation is now at a critical timepoint.

Patients with metastatic breast cancer who are eligible to receive pertuzumab have been able to do so through the Cancer Drugs Fund: this is not an option for patients with metastatic melanoma. Should an immediate solution to this methodological issue not be found, the Committee must take these circumstances into account when coming to a recommendation in this appraisal.

Conclusion

Cobimetinib + vemurafenib offers further improvement for the lives of a subgroup of patients with metastatic or unresectable melanoma; those presenting as BRAFV600 mutation-positive. Compared to the current standard of care (monotherapy treatment with a BRAF inhibitor), cobimetinib combination further delays disease progression, increases overall survival and reduces BRAF-inhibitor mediated toxicity.

The clinical benefit observed with cobimetinib + vemurafenib allows patients to remain on treatment for longer, thus deriving benefit for longer.

Standard NICE methodology does not allow cobimetinib to be cost-effective at any positive price. An immediate solution is needed to resolve this methodological perversity, and this should be taken into account by the Committee when coming to a recommendation.

Table 3 Base-case results, excluding PAS, for direct treatment comparison.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Cobimetinib + vemurafenib	£163,974*	4.015	3.034					£163,974
Vemurafenib monotherapy	£81,984	3.392	2.489	£81,990	0.622	0.545	£150,514	£81,984
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years * Time on treatment results from the coBRIM study were utilised for the direct comparison of cobimetinib + vemurafenib vs vemurafenib.								

Table 4 Base-case results, excluding PAS for indirect treatment comparison

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Cobimetinib + vemurafenib	£208,047*	4.015	3.034					£208,047
Dabrafenib	£78,392	3.281	2.417	£129,655	0.733	0.618	£209,942	£78,392
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years * For the indirect comparison of cobimetinib + vemurafenib vs. dabrafenib, PFS was used as a proxy for time on treatment, due to availability of data. As such, there is a difference in total costs with cobimetinib + vemurafenib across the two comparisons presented in Table 3 and Table 4.								

2. The technology

2.1 Description of the technology

2.1.1 Give the brand name, UK approved name, the therapeutic class and a brief overview of the mechanism of action.

Cobimetinib (brand name: Cotellic), is an antineoplastic agent targeting the MEK enzyme in the MAPK pathway.

This pathway includes multiple enzymes and communicates signals from the cell surface resulting in cell proliferation and survival. BRAF enzyme is found within the MAPK pathway, and is mutated in around 40% of patients with melanoma (Lee, 2011). This mutation results in inappropriate pathway activation leading to excessive cell proliferation and survival.

Vemurafenib is an oral therapy which selectively targets the BRAF enzyme, inhibiting its action and the MAPK pathway. However MAPK pathway reactivation can occur via the MEK1/2 enzymes.

Cobimetinib is a highly selective small molecule which blocks the MAPK pathway by targeting and binding the MEK 1/2 enzymes downstream of BRAF. This process inhibits phosphorylation of ERK1/2, therefore blocking cell proliferation and survival induced by the MAPK pathway.

Cobimetinib is given in combination with vemurafenib. This combination simultaneously targets mutated BRAFV600 proteins and MEK proteins in melanoma cells, resulting in stronger inhibition of intracellular signalling and decreased tumour cell proliferation and overcoming mechanisms of resistance to BRAF inhibition by vemurafenib.

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 Marketing authorisation for the indication detailed in this submission.

Positive Commission Decision for cobimetinib in combination with vemurafenib was received 20th November, 2015

2.2.2 Indication in the UK.

Cobimetinib is indicated for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation

2.2.3 Summarise any restrictions or contraindications included in the summary of product characteristics (SmPC).

There is one contraindication for use with cobimetinib: hypersensitivity to the active substance or to any of the excipients. For full details please see appendix 1

2.2.4 Include the SmPC for pharmaceuticals in an appendix.

The current SmPC can be found in appendix 1.

2.2.5 – 2.2.7 Regulatory approval

Cobimetinib received Commission Decision 20th November 2015 and was made commercially available in January 2016.

2.2.8 State whether the technology has regulatory approval outside the UK. If so, please provide details.

Cobimetinib received EU approval. It is also approved for use in Switzerland and the USA.

2.2.9 State whether the technology is subject to any other health technology assessment in the UK. If so, give the timescale for completion.

No ongoing health technology appraisals

2.3 Administration and costs of the technology

2.3.1 Costs of the technology being appraised

Please see Table 5

2.3.2 Provide details of any patient access scheme

No patient access scheme for cobimetinib is currently in place, or under consideration by the Department of Health. An existing patient access scheme is in place for vemurafenib.

2.3.3 For devices, provide the list price and average selling price

n/a

Table 5 Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	White, round film-coated tablets of approximately 6.6 mm diameter, with “COB” debossed on one side.	SmPC
Acquisition cost (excluding VAT) *	£4275.67 (pack) £4645.06 (month)	
Method of administration	Oral use. The tablets should be swallowed whole with water	SmPC
Doses	The recommended dose of cobimetinib is 60 mg (3x20mg tablets) once daily. Doses are on a 28 day cycle. 3 x 20mg tablet taken once daily for 21 consecutive days, followed by a 7 day treatment break Each treatment cycle should recommence following the 7-day treatment break.	SmPC
Dosing frequency	60mg taken daily on days 1 to 21; followed by a 7 day break (Days 22 to 28). Subsequent treatment cycles should start after the 7-day treatment break has elapsed. Treatment with cobimetinib should continue until patients no longer derive benefit or unacceptable toxicity	SmPC
Average length of a course of treatment	Patients should remain on treatment until disease progression or unacceptable toxicity	SmPC
Average cost of a course of treatment	The list price for one pack of 63 x 20mg cobimetinib tablets is £4,275.67	
Anticipated average interval between courses of treatments	Each 28 day treatment cycle includes 21 days of active treatment, followed by a 7 day break. The 28 day cycle is continuous until disease progression, at which point treatment with cobimetinib stops permanently.	SmPC
Anticipated number of repeat courses of treatments	Patients should remain on treatment until disease progression or unacceptable toxicity	SmPC
Dose adjustments	Decision on dose adjustments for management of adverse events is at the prescriber discretion. The following recommended dose modifications are for guidance:	SmPC

	Grade (CTC-AE)*	**Recommended cobimetinib dosage**	
	Grade 1 or Grade 2 (tolerable)		
		No dose reduction. Maintain cobimetinib at a dose of 60 mg once daily (3 tablets)	
	Grade 2 (intolerable) or Grade 3/4		
	1st Appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 40 mg once daily (2 tablets)	
	2nd Appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 20 mg once daily (1 tablet)	
	3rd Appearance	Consider permanent discontinuation	
Anticipated care setting	Treatment with cobimetinib in combination with vemurafenib should only be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products, as such treatment will be initiated in the secondary care setting only and self-administered by patients at home.		SmPC

2.4 Changes in service provision and management

2.4.1 State whether additional tests or investigations are needed

Cobimetinib is a targeted therapy, used only as an adjunct to concomitant vemurafenib treatment, and as such is indicated for use in patients who have BRAF V600 mutation-positive unresectable or metastatic melanoma, confirmed by a validated test. BRAF mutation testing is part of routine management for patients with advanced melanoma in the UK, therefore is not considered an additional cost or resource burden

2.4.2 Identify the main resource use to the NHS associated with the technology being appraised.

Treatment with cobimetinib in combination with vemurafenib should only be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products. As such it is anticipated treatment will be in specialist secondary, or tertiary care centres only. Cobimetinib and the concomitant vemurafenib are oral tablets so will not impact infusion or administration suites at these centres.

2.4.3 Specify if the technology requires additional infrastructure in the NHS to be put in place.

Cobimetinib and the concomitant vemurafenib are oral tablets so will not impact infusion or administration suites at specialist secondary or tertiary centres. As per section 2.4.4, monitoring requirements for cobimetinib are not anticipated to require additional resource.

As such, no additional infrastructure is required for administration and monitoring of treatment with cobimetinib..

2.4.4 State if and to what extent the technology will affect patient monitoring compared with established clinical practice in England.

Monitoring and dose adjustments may be required to manage certain adverse events. However this is not considered additional resource as compared to established clinical practice in England and Wales.

2.4.5 State whether there are any concomitant therapies specified in the marketing authorisation or used in the key clinical trials (for example, for managing adverse reactions) administered with the technology.

Cobimetinib is administered in combination with vemurafenib. Cobimetinib is not licensed for use as a monotherapy agent, or in combination with any other systemic anti-cancer therapies.

2.5 Innovation

The combination of cobimetinib and vemurafenib is a further step-change in the management of BRAF V600 mutation-positive advanced melanoma, adding to the significant improvement in PFS, OS and health-related quality of life (HRQoL) already seen with vemurafenib.

There is a strong scientific and clinical rationale for the addition of cobimetinib to vemurafenib, with the added mechanism of action offering inhibition of MEK. This is a rare example in which development of a second targeted agent is specifically to

enhance the activity of the existing agent; vemurafenib. This has been possible through exploiting knowledge of resistance mechanisms and signalling pathways.

Until the introduction of vemurafenib, the standard systemic treatment for inoperable melanoma was dacarbazine – a non-specific cytotoxic agent that induced some degree of tumour regression in only about 15% of cases, and has never been demonstrated to improve overall survival in a randomised trial

However, advances in treatment of stage IV melanoma have progressed rapidly in the last 3 years through the availability of targeted therapies, and more recently immunotherapies. As highlighted in TA 269, these options have caused a step-change in the management of patients with advanced melanoma. New treatment options are predicted to further develop clinical management of patients.

The relatively young average age of patients with metastatic melanoma means they are likely to be of working age. The personal and wider societal benefit derived through prolonging patient survival and slowing disease progression is not currently captured in the QALY calculation.

Cobimetinib + vemurafenib are oral medications, thus providing patient choice and flexibility for administration. These patient benefits of treatment are not currently captured in the model and QALY calculation.

We consider cobimetinib + vemurafenib to be an innovative treatment, with significant positive impact on patients' lives.

3. Health condition and position of the technology in the treatment pathway

3.1 *Provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.*

Malignant melanoma is a tumour which arises from melanocytic cells and primarily involves the skin. Tumours may arise de novo or from pre-existing skin naevi (moles). Individuals with large numbers of common naevi and those with congenital naevi, multiple naevi, and/or atypical naevi (dysplastic naevi) are at greater risk. The inheritance of melanoma is polygenic, with 5 to 10% of melanomas appearing in melanoma-prone families. In addition to these genetic factors, the risk factors are skin which tends to burn in the sun, having many moles, intermittent sun exposure and sunburn. Most melanomas occur in people with pale skin.

Approximately 90% of melanomas are diagnosed as primary tumours without any evidence of metastasis. In its early stages, melanoma is normally asymptomatic and can often be cured by surgery (resection). The tumour-specific 10-year-survival for such tumours is 90% (CRUK,[a]).

However, the tumour may spread or metastasise to nearby lymph nodes (stage III) or to other parts of the body (stage IV). Around 10% of patients have metastatic disease at diagnosis or relapse with metastatic spread after treatment for apparently localised disease. Survival for patients with metastatic disease is very poor with 5 year survival of 10% for stage IV disease (CRUK, [a]). Patients with uncontrolled (i.e. progressive) metastatic disease are generally very symptomatic with a consequently low quality of life (Cornish 2009).

In 2011, there were 11,121 new cases of malignant melanoma in England. In the UK, about 27% of people diagnosed with melanoma are younger than 50 years. At diagnosis, around 1% of melanomas are stage IV (CRUK,[b]).

A mutated form of the BRAF gene (called BRAF V600) is found in about 40% of melanomas. The mutated gene means cells produce excessive BRAF protein, leading to uncontrolled cell division and growth of the tumour.

3.2 Describe the effects of the disease or condition on patients, carers and society.

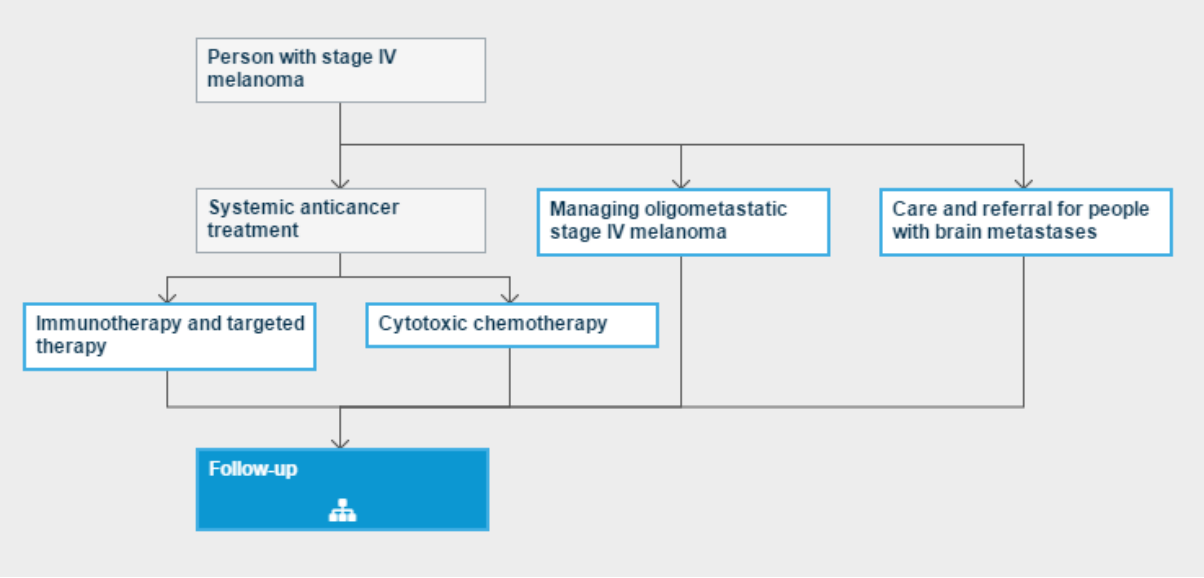
A systematic review of quality of life studies in melanoma, (Cornish, 2009) noted that the immediate period following diagnosis was often associated with impairment in HRQoL, with patients reporting increased pain, less energy and physical or emotional distress which impaired social functioning. Two more recent UK studies showed that melanoma patients currently have significant unmet needs, irrespective of melanoma stage mainly in the psychosocial support, information/education, and physical health domains, contributing and leading not uncommonly to anxiety and depression (Molassiotis, 2014; Stamataki 2014).

The societal impact of metastatic melanoma is substantial, with the total societal cost due to malignant melanoma in England, in 2002, estimated at £138 million (Morris 2008). The relatively young average age of patients with metastatic melanoma means they are likely to be of working age. Research from 2002 suggests 15.1% of the total costs of malignant melanoma are due to indirect morbidity costs, with 67.6% due to indirect mortality costs (Morris 2008).

3.3 Clinical pathway of care

Treatment options for advanced (unresectable or metastatic) melanoma depend on the person's BRAF mutation status and their treatment history. Figure 1 below is taken from the NICE Treatment Pathway (NICE Melanoma Pathway 2016). NICE TA guidance 269 and 321 recommend the BRAF inhibitors vemurafenib or dabrafenib respectively as options for treating BRAF V600 mutation-positive unresectable or metastatic melanoma.

Figure 1 Management of stage 4 melanoma (NICE Melanoma Pathway 2016)



NICE TA guidance 319 and 268 recommend ipilimumab, which is not a BRAF-targeted therapy, for untreated or previously treated advanced (unresectable or metastatic) melanoma. Recently two technology appraisals have been published for pembrolizumab: for treating advanced melanoma not previously treated with ipilimumab (TA366 2015) and for treating advanced melanoma after disease progression with ipilimumab (TA357 2015). Additionally a FAD (subject to appeal at time of this submission) was published in January 2016, recommending the use of nivolumab for treating advanced (unresectable or metastatic) melanoma (ID845 2016).

In clinical practice, for people with BRAF mutation-positive advanced melanoma, a BRAF inhibitor is the usual first-line treatment; ipilimumab and pembrolizumab may be considered for first-line use in a subgroup of patients who are relatively well and in whom the disease is not progressing rapidly. As such the treatment pathway will remain the same and patients who would have previously been prescribed vemurafenib (or dabrafenib) will now be prescribed vemurafenib in combination with cobimetinib.

3.4 Life expectancy of people with the disease or condition in England

See section above (3.1)

3.5 Relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being used.

The following are existing NICE guidelines, pathways and technology appraisals relevant to this appraisal.

- Melanoma NICE Pathway
- NICE Guidelines NG14 Melanoma: assessment and management
- Nivolumab for treating advanced (unresectable or metastatic) melanoma (ID845 2016)
- Technology appraisal guidance 268, Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. December 2012
- Technology appraisal guidance 269, Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. December 2012
- Tehnology appraisal guidance 319, Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. July 2014
- Technology appraisal guidance 321, Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. October 2014
- Technology appraisal guidance 357. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab October 2015
- Technology appraisal guidance 366. Pembrolizumab for advanced melanoma not previously treated with ipilimumab. November 2015

3.6 Details of other clinical guidelines and national policies.

There are no current up to date UK guidelines outside of the latest NICE Melanoma guidance (NG14 2015).

3.7 Describe any issues relating to current clinical practice, including any variations or uncertainty about established practice.

See section above (3.3)

3.8 Equality

Roche does not believe that the use of cobimetinib (in combination with vemurafenib) will be associated with any equality issues.

4. Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Search strategy overview.

Methodology and objective

A systematic literature review was conducted to identify all relevant published and unpublished RCT evidence relating to the efficacy of cobimetinib in combination with vemurafenib when used in the treatment of adults with unresectable or metastatic BRAF V600 mutation-positive melanoma.

The systematic literature review was conducted according to the NICE guide to the methods of technology appraisal 2013 and therefore adhered to the Centre for Reviews and Dissemination guidance for undertaking systematic reviews in health care.

Search strategy

4.1.2 Search strategy details.

The complete search strategy for this review is provided in Appendix 2. The following sources were searched, using search terms that combined population, interventions and study types:

- Electronic databases were searched from database inception to 8th September 2015, except for Embase Alert which was searched to 9th September 2015
    - Embase (Ovid SP)
    - MEDLINE and MEDLINE In-Process (Ovid SP)
    - Embase Alert (ProQuest)
    - Cochrane Central Library of Controlled Trials (Cochrane Library)
- Congress proceedings were also searched manually for the most recent 2 years
    - American Society of Clinical Oncology (ASCO) Annual Meeting (2015 and 2014 meetings)

- European Society for Medical Oncology (ESMO) Congress (2014 meeting)
- Society for Melanoma Research (SMR; 2014 and 2013 meeting)

- The reference list of included articles were hand-searched for potentially relevant studies

Study selection

4.1.3-4.1.4 Inclusion and exclusion selection criteria, language restrictions and study selection. Flow diagram of studies included and excluded at each stage.

The eligibility criteria used for the systematic review are presented in Table 6. No language restrictions were applied.

Table 6. Eligibility criteria for systematic literature review of RCT evidence

Domain	Inclusion criteria	Exclusion criteria
Population	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma	Studies that do not include the patient population of interest, or that do not present relevant outcomes for the population of interest separately to outcomes for other patients
Interventions	Cobimetinib in combination with vemurafenib	Cobimetinib monotherapy
Comparators	Dabrafenib monotherapy Vemurafenib monotherapy	-
Outcomes	Progression-free survival Overall survival Response rate Adverse effects of treatment Health-related quality of life	Pharmacokinetic outcomes
Study design	Phase II, III or IV RCTs Systematic reviews/meta-analyses of RCTs	Phase I clinical trials Narrative or non-systematic reviews Case studies and case reports
Other considerations	Only publications on human subjects will be included	-

1) **Review strategy**

The following review process was followed:

- Title/abstract review

Each abstract was reviewed against the inclusion/exclusion criteria by two independent reviewers. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. Any discrepancies between the two independent reviewers were resolved by a third independent reviewer making the final decision.

- Full-text review

  Each full-text article was reviewed against the inclusion/exclusion criteria by two independent reviewers, who came to a consensus on the included articles. In cases where the article did not give enough information to be sure if it met the inclusion criteria, the article was excluded to ensure that only relevant articles were ultimately included in the systematic review. The results of the two reviewers were compared and any disagreements resolved by discussion until a consensus was met.

- Data extraction

  The methods and results of all included studies were extracted into pre-specified data extraction tables in Microsoft Word by a single reviewer who also assessed study quality. A second independent reviewer then independently verified the extracted information, checked that no relevant information had been missed and also assessed study quality. Any discrepancies or missing information identified by the second individual were discussed by both individuals until a consensus was reached on the information that should be presented in the extraction tables.

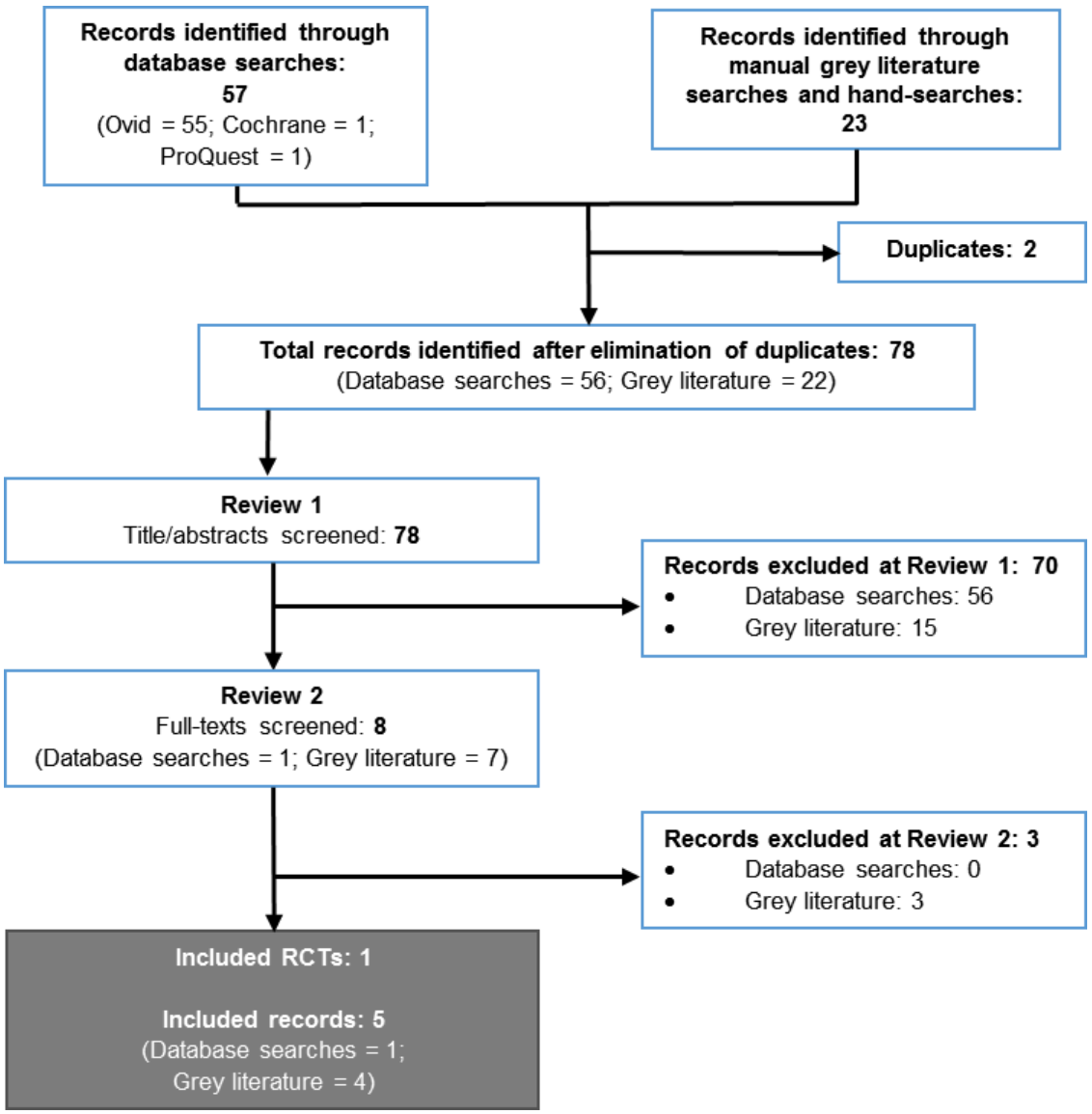
2) Search results

The electronic database search (Appendix 2, accessed 8th or 9th September 2015) identified 57 records and searches of conference proceedings and reference lists identified 23 records; in total, 78 records (56 database abstracts, 22 conference abstracts) were screened after de-duplication of results. Of these, 70 records were excluded based on the screening of the title/abstract. On re-application of the review eligibility criteria to the remaining full-text articles, 5 records were ultimately included

in the review, which all reported outcomes of the same RCT (coBRIM; see Table 68 in Appendix 3).

The three records excluded from the systematic review at the full-text review stage can be found listed in Table 69 in Appendix 3; two were congress abstracts relating to coBRIM (pharmacokinetic outcomes; outcomes subsequently presented in the peer-reviewed publication), and the other was a congress abstract relating to a systematic review and meta-analysis in which outcomes for cobimetinib in combination with vemurafenib were not presented specifically.

Figure 2. PRISMA diagram for systematic literature review of RCTs (search cut-off date: 8th or 9th September 2015)



4.1.5 Study publication sources.

One RCT was identified – the coBRIM study. The list of all eligible publications can be found in Table 68 in Appendix 3

4.1.6 Provide a complete reference list for excluded studies in an appendix.

No identified studies were excluded.

4.2 List of relevant randomised controlled trials

4.2.1 Relevant RCTs comparing the intervention with other therapies.

Table 7. List of relevant RCTs

Trial number (name)	Sponsor	Intervention	Comparator	Population	Primary study reference
NCT01689519 (CoBRIM)	F. Hoffmann–La Roche / Genentech	Oral vemurafenib 960 mg twice daily on Days 1−28 and oral cobimetinib 60 mg once daily on Days 1−21 of each 28-day treatment cycle	Oral vemurafenib 960 mg twice daily on Days 1−28 and oral placebo once daily on Days 1−21 of each 28-day treatment cycle	Adults at least 18 years of age with previously untreated $BRAF^{V600}$ mutation-positive unresectable locally advanced stage IIIC or stage IV melanoma	Larkin et al. 2014 (Larkin 2014): data cut-off date: 9th May 2014 Updated results of the PFS and ORR analyses are presented in Larkin et al. 2015 (Larkin 2015): data cut-off date: 16th January 2015 Updated, and final OS results presented by Atkinson et al. at the 2015 SMR congress (Atkinson 2015). Data cut August 2015.

4.2.2 RCTs excluded.

The efficacy and safety of cobimetinib in combination with vemurafenib have been compared to placebo in combination with vemurafenib in one phase III, randomised,

double-blind controlled trial (coBRIM). No further trials comparing the efficacy and safety of cobimetinib in combination with vemurafenib with relevant comparators were found. A summary of the identified RCT is provided in Table 7.

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1 Items 3 to 6b of the CONSORT checklist should be provided for all RCTs listed:

The regulatory submission which forms the basis of the EMA's regulatory approval for cobimetinib in combination with vemurafenib, for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, is based primarily on the coBRIM study (along with relevant supporting pre-clinical data).

The final analysis of the primary endpoint of PFS was conducted on 9 May 2014, and is the data set on which the Clinical Study Report (CSR) and the New England Journal of Medicine (NEJM) primary publication (Larkin 2014) are based.

A further safety analysis of the data was conducted to support the US New Drug Application (NDA) and was published at the Society for Melanoma Research (SMR) Annual Meeting 2014 (Dreno 2014). An exploratory efficacy analysis of the data took place, at the request of the EU assessors, one year after enrollment of the last patient with a clinical data cutoff of 16 January 2015 and forms the basis of the cobimetinib Summary of Product Characteristics (SmPC). Efficacy endpoints from this data cut were presented at ASCO 2015 (Larkin 2015).

The final analysis of the secondary endpoint of OS was conducted on 8 Aug 2015, and was published at the SMR Annual Meeting 2015 (Atkinson 2015). This abstract was not identified in the SLR as publication occurred after SLR completion. However, it is included in the submission as it is the final analysis of OS.

Table 8 - Dates of conducted analyses

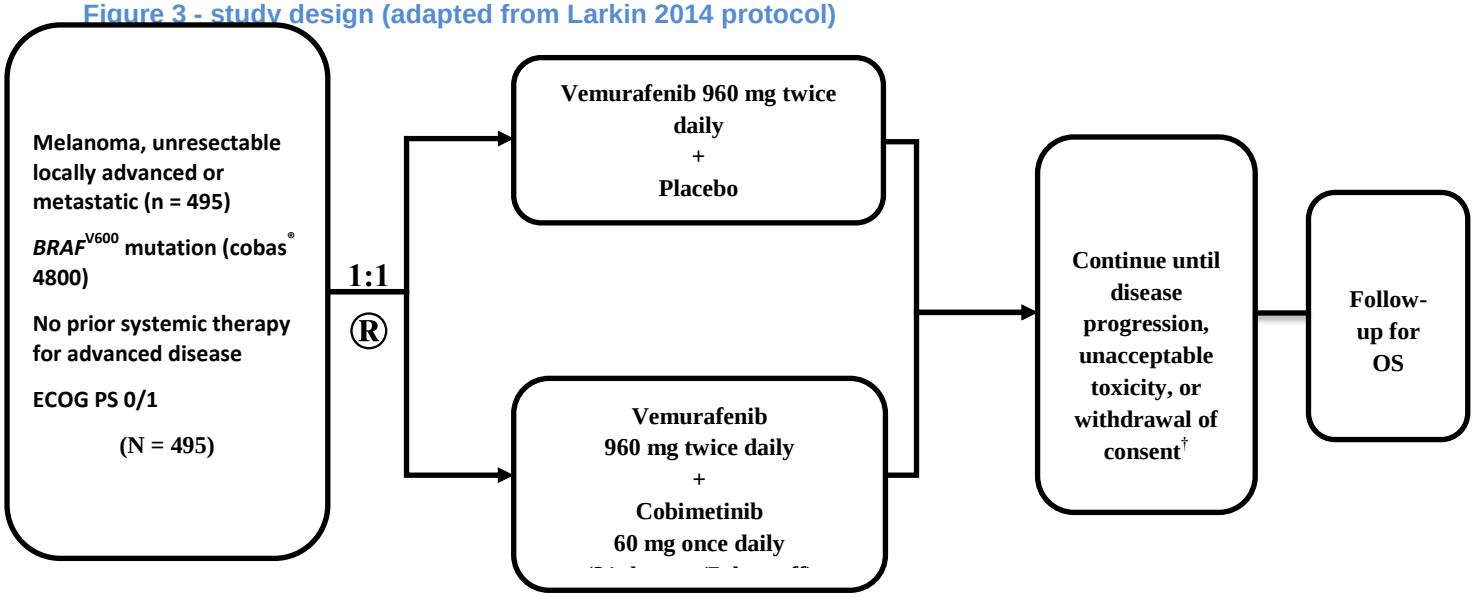
Conducted and planned analyses	Data cutoff dates	Publications
Primary Endpoint Primary analysis of PFS Updated analysis of PFS	9th May 2014 16th January 2015	Larkin et al NEJM 2014, SmPC Larkin et al ASCO 2015, SmPC

Secondary endpoints		
Overall Survival		
1st interim analysis of OS	9th May 2014	Larkin et al NEJM 2014, SmPC
2nd interim analysis of OS	16th January 2015	Larkin et al ASCO 2015, SmPC
Final analysis of OS	28th August 2015	Atkinson et al SMR 2015
Response rates		
Primary analysis	9th May 2014	Larkin et al NEJM 2014
Updated analysis	16th January 2015	Larkin et al ASCO 2015
Safety analyses		
Primary analysis	9th May 2014	Larkin et al NEJM 2014
Updated analysis	19th September 2014	Dreno et al SMR 2014
Final analysis	[redacted]	To be advised

CoBRIM TRIAL DESIGN

Study GO28141 (coBRIM) is a multicentre, randomised, double-blind, placebo-controlled, Phase III study designed to evaluate the safety and efficacy of cobimetinib used in combination with vemurafenib as compared to vemurafenib alone, in patients with BRAF V600 mutation-positive unresectable locally advanced (Stage IIIc) or metastatic melanoma (Stage IV) (Larkin 2014).

Figure 3 - study design (adapted from Larkin 2014 protocol)



†Crossover between treatment groups not allowed

ECOG: Eastern Cooperative Oncology Group; OS: Overall Survival; R: Randomisation

A total of 495 eligible patients were randomised in a 1:1 ratio to receive treatment with one of the following regimens:

• Arm A (control arm): vemurafenib 960 mg by mouth (PO) twice daily (BID) on days 1−28 and placebo PO once daily (QD) on days 1−21 of each 28-day treatment cycle

• Arm B (investigational arm): vemurafenib 960 mg PO BID on Days 1−28 and cobimetinib 60 mg PO QD on Days 1−21 of each 28-day treatment cycle

The stratified, permuted-block randomisation scheme was used for treatment allocation based on the following stratification factors:

• Geographic region (North America, Europe, Australia/New Zealand/others)

• Metastatic classification (unresectable Stage IIIc, M1a, and M1b; or M1c)

The investigator, patient, and Sponsor were blinded to treatment assignment (Larkin 2014).

ELIGIBILITY CRITERIA

The study population for this trial comprised treatment-naïve adult patients with unresectable, locally advanced Stage IIIc or metastatic melanoma as defined by the American Joint Committee on Cancer (AJCC) classification v.7 (Larkin 2014). Only patients harbouring the BRAF V600 mutation were included. This represents the population for which vemurafenib is indicated. The cobas® 4800 BRAF V600 mutation test was used to determine the presence of the BRAF V600 mutation. Prior adjuvant therapy was permitted, provided such treatment did not include a BRAF or a MEK inhibitor. Brain metastasis is common in advanced melanoma and patients with treated and stable brain metastases were eligible for randomisation. This is consistent with standard clinical practice. Table 9 and
Table 10 contain full details of the inclusion and exclusion criteria for the study.

Table 9 - Inclusion Criteria (Larkin 2014)

Inclusion criteria
• Patients with histologically confirmed melanoma, either unresectable stage IIIc or stage IV metastatic melanoma, as defined by the American Joint Committee on Cancer 7th edition. Unresectability of stage IIIc disease must have confirmation from a surgical oncologist • Patients must be naïve to treatment for locally advanced unresectable or metastatic disease (i.e., no prior systemic anti-cancer therapy for advanced disease; stage IIIc and IV). Prior adjuvant immunotherapy (including ipilimumab) is allowed • Documentation of BRAF V600 mutation-positive status in melanoma tumour tissue (archival or newly obtained tumour samples) using the cobas® 4800 BRAF V600 mutation test • Measurable disease per response evaluation criteria in solid tumours (RECIST) v1.1. • Eastern Clinical Oncology Group performance status of 0 or 1 • Consent to provide archival tissue for biomarker analyses • Consent to undergo tumour biopsies for biomarker analyses • Male or female patient aged ≥18 years • Life expectancy ≥12 weeks • Adequate haematologic and end organ function

Table 10 - Exclusion criteria (Larkin 2014)

Exclusion criteria
• History of prior RAF or MEK pathway inhibitor treatment • Palliative radiotherapy within 14 days prior to the first dose of study treatment • Major surgery or traumatic injury within 14 days prior to first dose of study treatment • Active malignancy other than melanoma that could potentially interfere with the interpretation of efficacy measures. Patients with a previous malignancy within the past 3 years are excluded except for patients with resected basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) of the skin, melanoma in-situ, carcinoma in-situ of the cervix, and carcinoma in-situ of the breast • History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment, retinal vein occlusion (RVO), or neovascular macular degeneration • Uncontrolled glaucoma with intra-ocular pressures >21mmHg • Serum cholesterol ≥Grade 2 • Hypertriglyceridemia ≥Grade 2 • Hyperglycemia (fasting) ≥Grade 2 • History of clinically significant cardiac dysfunction • Patients with active CNS lesions (including carcinomatous meningitis) are excluded. However, patients are eligible if: - All known CNS lesions have been treated with stereotactic therapy or surgery, AND - There has been no evidence of clinical and radiographic disease progression in the CNS for ≥3 weeks after radiotherapy or surgery • Current severe, uncontrolled systemic disease • History of malabsorption or other condition that would interfere with absorption of study drugs • Pregnant, lactating, or breast feeding

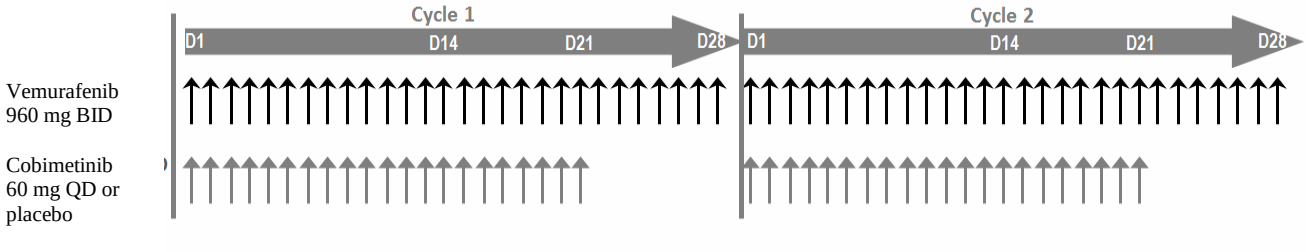
LOCATIONS WHERE THE DATA WERE COLLECTED

From January 2013 through January 2014, 495 patients were enrolled at 135 sites in the United States, Canada, Australia, New Zealand, Europe, Russia, Turkey, and Israel (Larkin 2014). Eleven UK centres enrolled a total of 29 patients.

TRIAL DRUGS AND CONCOMITANT MEDICATIONS

The dosing schedule for the two arms is shown in Figure 4.

Figure 4 - CoBRIM dosing scheme (Larkin 2014)



The cobimetinib 60mg dose, or corresponding placebo, was taken as three tablets orally once daily starting on Day 1 through Day 21 of each 28-day treatment cycle (see Figure 4). Patients were instructed to take the cobimetinib/placebo dose at approximately the same time each day, preferably in the morning with the vemurafenib dose to facilitate pharmacokinetic assessments during the study. Study drugs were to be taken with a glass of water, with or without a meal. Vemurafenib was taken orally at a starting dose of 960mg (4 tablets) BID, beginning on Day 1 and continuing through Day 28 of each 28-day treatment cycle (see Figure 4). Patients were instructed to take the first dose of vemurafenib in the morning, and the second dose in the evening.

Permitted concomitant therapy included oral contraceptives, hormone-replacement therapy, or maintenance therapy and pain relief. Prophylactic administration of anti-emetics and anti-diarrhoeal medications and haematopoietic growth factors were not permitted before initial treatment with study drugs. However, at the discretion of the investigator, prophylactic anti-emetic and anti-diarrhoeal medication(s) were permitted before subsequent doses of study drugs.

Prohibited therapy included any prior or concomitant therapy intended for the treatment of advanced melanoma, either approved by health authorities or experimental, including chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy, or investigational agents. Prior adjuvant immunotherapy was permitted. Palliative radiotherapy or major surgery within 14 days prior to first dose of study treatment was prohibited.

PRIMARY, SECONDARY AND TERTIARY OUTCOMES

This study was conducted in accordance with the principles of the “Declaration of Helsinki” and adhered to the principles outlined in the International Conference on Harmonisation (ICH) “Guideline for Good Clinical Practice” (GCP) Tripartite Guideline (January 1997), or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual (Larkin 2014).

The outcomes and measures employed in coBRIM are commonly accepted endpoints and are currently used widely in oncology studies.

Primary Efficacy Outcome Measure

Progression-free survival

Progression-free survival is accepted as a reliable endpoint and is widely used as a primary endpoint/outcome measure in clinical trials when investigating a treatment effect in oncology studies.

PFS was defined as the time from randomisation to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever comes first. Although the primary efficacy endpoint is investigator-assessed PFS, PFS based on independent review committee (IRC) assessments was also analysed to support the primary analysis.

Secondary Efficacy Outcome Measures

Overall survival

OS has long been established as a standard endpoint/outcome measure used in oncology clinical trials and has been used as a primary or secondary endpoint/outcome measure depending on the stage of cancer under investigation.

Overall survival was defined as the time from randomisation to death from any cause.

Objective response rate

Objective response has been utilised as a secondary endpoint/outcome measure extensively and is considered robust supportive evidence for PFS and OS outcomes in evaluating a treatment effect in patients. The RECIST response criteria ensure a high degree of uniformity in response assessment by different reviewers.

Objective response rate for patients with measurable disease at baseline was defined as complete or partial response as assessed by investigator according to RECIST v1.1.

Best overall response rate (BORR)

Best overall response (confirmed) was defined as a complete response (CR) or partial response (PR) per RECIST v1.1. The best overall response of CR or PR was determined by two consecutive investigator assessments that were performed four or more weeks apart. In the case of stable disease (SD), measurements had to meet the SD criteria at least once after randomisation at a minimum interval not less than 6 weeks (CSR).

Duration of response

Duration of response was evaluated for patients who satisfied the criteria for BORR (confirmed). Duration of response was defined as the time from first occurrence of a documented confirmed objective response until the time of disease progression, as determined by investigator review of tumour assessments with use of RECIST v1.1 or death from any cause during the study (CSR).

Progression-free survival

Although the primary efficacy endpoint is investigator-assessed PFS, PFS based on independent review (two board certified radiologists) was also analysed to support the primary analysis.

Safety Outcome Measures

Safety assessments consisted of monitoring and recording adverse events (AEs), including serious adverse events (SAEs) and non-serious adverse events of special interest (AESIs), protocol-specified safety laboratory assessments, vital signs, and

other protocol-specified tests that were deemed critical to the safety evaluation of the study.

The following safety parameters were summarised by treatment arm: all AEs, drug related AEs, deaths, SAEs, drug-related SAEs, AESIs, and AEs leading to dose interruption/modification and to discontinuation of study treatment. For classification purposes, the Sponsor assigned preferred terms to the verbatim terms reported on the Case Report Form (CRF) using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA 16.1) terminology for AEs (CSR).

Patient-Reported Outcome (PRO) Measures

The PRO measures were the European Organisation for Research and Cancer [EORTC] Quality of Life Questionnaire [QLQ-C30] (EORTC QLQ-C30) and EuroQol's 5 dimension 5 level (EQ-5D-5L) Questionnaire. The PRO questionnaires (EORTC QLQ-C30 and EQ-5D-5L) were supplied in the local language(s) of each participating country (Larkin 2014 protocol). The HRQoL, EORTC QLQ-C30 is included to characterise the impact of treatment on patients while receiving and following vemurafenib and cobimetinib exposure (CSR).

The EORTC QLQ-C30 is a validated and reliable self-reported measure of quality of life for patients with cancer who are receiving cancer treatment and has been used widely in oncology clinical trials including trials focusing on patients with metastatic or advanced melanoma. The questionnaire consists of 30 questions that incorporate 5 functional domains (physical, role, cognitive, emotional, and social), a global health status/global quality of life measure; 3 symptom scales (fatigue, pain, and nausea and vomiting), and 6 single items that assess additional symptoms (dyspnoea, appetite loss, sleep disturbance, constipation, diarrhoea, and the perceived financial burden of treatment experienced by patients with cancer).

The EQ-5D-5L is a generic, preference-based health utility measure with questions that span 5 dimensions of life, for which patients assign one of 5 levels of severity. This builds a composite of the patient’s health status. Applicable to a wide range of health conditions and treatments, EQ-5D-5L provides a simple descriptive profile and

a single index value for health status. The use of the EQ-5D-3L and EQ-5D-5L in cancer has increased in recent years.

In addition to the outcomes cited above, pharmacokinetic analyses have been conducted. Exploratory biomarker analyses in tumour tissue were conducted with the goal of exploring the intrinsic and acquired mechanisms of resistance to MEK and BRAF inhibition, the association of biomarkers with efficacy and/or AEs, and the further understanding of disease biology (CSR). The results of these analyses are not included in the submission.

4.3.2 Provide a comparative summary of the methodology of the RCTs in a table.

Only one RCT was identified, with the methodology summarised in Table 7 and Table 8.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1-4.4.2 Trial population included in primary analysis of the primary outcome, and methods used to take account of missing data

The statistical hypothesis of the coBRIM study is as follows:

H_0: PFS(Arm A) =PFS(Arm B) versus H_1: PFS(Arm A) ≠ PFS(Arm B)

where PFS(Arm A) represents the survival function of PFS in the vemurafenib + placebo arm and PFS(Arm B) represents the survival function of PFS in the vemurafenib + cobimetinib arm (Larkin 2014).

Determination of sample size and power

Enrollment of 500 patients was planned for the study. Statistical considerations were based on the following assumptions:

• Stratified log-rank test at 0.05 significance level (2-sided)

• 6 months median PFS for the vemurafenib + placebo arm

• 11 months median PFS for the vemurafenib + cobimetinib arm

• Accrual ramp-up time of 9 months to reach 65 patients per month thereafter for a total enrollment period of approximate 14 months

• 5% dropout rate

• No interim analysis of PFS

A total of 206 PFS events provides >95% power to detect an improvement in median PFS from 6 months in the vemurafenib + placebo arm to 11 months in the vemurafenib + cobimetinib arm (corresponding to a hazard ratio of 0.55, and the minimal detectable difference [MDD] is 0.76). The pre-specified number of progression events (206 events) was reached in May 2014 and the database locked for data analysis on July 10, 2014.

The final analysis of OS was to be performed after the occurrence of approximately 385 deaths. A total of 385 deaths was estimated to provide approximately 80% power to detect an improvement in median OS from 15 months in the vemurafenib + placebo arm to 20 months in the vemurafenib + cobimetinib arm (corresponding to a hazard ratio for death of 0.75).

Analysis Populations

The primary analysis population for the efficacy endpoints is the intent-to-treat (ITT) population, defined as all randomised patients, regardless of whether or not study treatment is received. Data for patients in the ITT population were analysed according to the treatment assigned.

The safety population includes all patients who received at least one dose of study treatment and were analysed according to the treatment received.

The PRO population includes all patients who have a baseline assessment and at least one post-baseline assessment. The PRO population was analysed according to the treatment assigned at randomisation (i.e., ITT) (CSR).

INTERIM ANALYSIS

No interim analyses of the primary endpoint (PFS) were planned or performed.

Three OS analyses (2 interim analyses and the final analysis) were performed (see Table 11):

1. The first OS interim analysis was performed at the time of the final PFS analysis (9 May 2014 data cutoff).

2. The second OS interim analysis was performed at the request of the EU assessors, one year after enrolment of the last patient (16 Jan 2015 data cutoff).

3. The final OS analysis was performed in accordance with the study design, after the occurrence of approximately 385 deaths. At this time, there was a median follow-up of 18.5 months (28 August 2015 data cutoff).

Table 11 Assumptions and characteristics of the interim and final analyses for OS (CSR)

Overview	
HR targeted Targeted median (vemurafenib + placebo) Targeted median (vemurafenib + cobimetinib) Projected enrollment period	0.75 15 months 20 months 13.7 months
First interim OS **(to be performed at time of final PFS analysis)**	
Estimated cutoff date[a] Projected number of events (% of final events) Projected MDD[b] (p--value)	16 months after FPI 115 (30%) 0.48 (< 0.000085)
Second Interim OS	
Number of events (% of final events) Estimated cutoff date[a] Projected MDD[b] (p--value)	256 (67%) 27 months after FPI 0.73 (<0.012)
Final OS	
Number of events (% of final events) Estimated cutoff date[a] Projected MDD[b] (p--value) Power Overall α level (2-sided)	385 (100%) 46 months after FPI 0.82 (<0.0463) 80% 0.05

FPI = first patient in; HR = hazard ratio; MDD = minimally detectable difference; OS = overall survival.
[a]Estimated data cutoff time from study enrollment date. Analysis results will be available after data cleaning.
[b]The largest observed HR that is projected to be statistically significant

EFFICACY ANALYSIS

Primary efficacy endpoint

Data from patients who had experienced disease progression or death were censored at the last tumour assessment date. Data from patients with no post-baseline tumour assessment were censored at the randomisation date. The primary analysis is a comparison of PFS between the two treatment arms and used a stratified log-rank test at an overall 0.05 significance level (2 sided). The hazard ratio for PFS was estimated using a stratified Cox model. Two-sided 95% confidence intervals (CIs) for the hazard ratio are provided. The stratified analyses incorporate 2 stratification factors: geographic region (North America, Europe, Australia/New

Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; M1c). Results from an unstratified log-rank test and the unstratified hazard ratio were presented. Kaplan-Meier methodology was used to estimate median PFS for each treatment arm, and the Kaplan-Meier curves are provided (Larkin 2014).

Sensitivity Analyses on the Primary efficacy endpoint

The following sensitivity analyses of PFS were performed (CSR):

• PFS non-stratified analysis: Non-stratified analyses of treatment effect (log-rank test and HR with use of a Cox proportional hazards model)

• PFS censored for non-protocol anti-cancer therapy: Patients who died or progressed after having received non-protocol anti-cancer therapy were censored at the date of the last evaluable tumour assessment prior to start of non-protocol anti-cancer therapy. Unstratified and stratified analyses of PFS were performed.

• PFS censoring accounting for missed visits: Patients who died or progressed after two or more consecutive missed visits were censored at the date of the last evaluable tumour assessment. Unstratified and stratified analyses of PFS were performed.

No data from the sensitivity analyses are included in the submission. Results from the sensitivity analyses showed no impact on the results from the primary analysis

Secondary endpoints

Overall Survival

Data for patients still alive at the time of analysis were censored at the date the patient was last known to be alive. Survival time for patients with no post baseline survival information was censored on the date of randomisation. The duration of OS was calculated as the date of death or censoring date minus the randomisation date plus 1 day. OS is compared between the two treatment arms with use of a two-sided stratified log-rank test at an overall two-sided 0.05 significance level. The HR for death is estimated using a stratified Cox model (CSR).

Objective response rate

Best overall response rate

Treatment difference in BORR was tested using a chi-square test with Schouten correction, and a 95% Hauck-Anderson CI was calculated for the difference in BORRs between treatment groups. In addition, a 95% Clopper-Pearson CI was calculated for the BORR (Larkin 2014).

Duration of response

Duration of response (DOR) was calculated only for patients who had a confirmed overall response of CR or PR. Median duration of response will be estimated using the Kaplan-Meier method, and the 95% CI was calculated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). Since the determination of DOR is based on a non-randomised subset of patients, formal hypothesis testing will not be performed on this endpoint.

Quality of life

Quality of life (QoL) analyses are post hoc with a pre-specified study population. The change from baseline in each domain score is assessed for each time point by treatment arm using descriptive statistics; formal statistical comparisons were not conducted. A responder analysis was also performed, which summarises the frequency of patients in each treatment arm who experienced clinically meaningful improvement (≥10-point change) at ≥1 post baseline assessment for each EORTC QLQ-C30 scale (symptoms, functional impact, and health-related QoL) (Dreno 2015).

Subgroup Analyses

Subgroup analyses were pre-planned for the study (CSR). The treatment effect of cobimetinib in combination with vemurafenib on PFS and OS was examined in subgroups defined by demographic and baseline characteristics and stratification factors to assess consistency. Because some subgroups could have small sample sizes, these analyses were considered exploratory.

The subgroups included the following:

- Disease stage (IIIc, M1a, M1b, M1c)
- Disease stage (IIIc/M1a/M1b, M1c)
- Age (≤ 65 years, > 65 years) at randomisation
- Race (non-White, White)
- Sex (female, male)
- Geographic region (North America, Europe, Australia/New Zealand/others)
- Eastern Cooperative Oncology Group performance status at randomisation (0, 1)
- LDH (normal, elevated)
- Presence of brain metastases (yes, no)
- Time since metastatic disease diagnosis (< 6 months, ≥ 6 months)
- Prior adjuvant therapy (Yes, No)
- BRAF V600 mutation status (V600E, V600K)

For PFS and OS, the Kaplan-Meier estimated median time to event was summarised by treatment arm for each of the subgroups defined above, as well as with an HR (treatment:control) estimated by unstratified Cox regression, which was displayed as a Forest plot

4.4.3 Statistical tests used in the primary analysis.

Table 12 - Summary of statistical analysis in coBRIM

Trial number (name)	CoBRIM (NCT01689519)
Hypothesis objective	To evaluate the efficacy and safety of vemurafenib in combination with cobimetinib, compared with vemurafenib and placebo, in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma, as measured by prolongation of PFS.
Statistical analysis	All the efficacy analyses were carried out in the intention-to-treat population. Rates of PFS and OS were estimated by the Kaplan-Meier method and compared by a stratified log-rank test. Response rates and 95% confidence intervals are reported for the two study groups. Differences in the response rate between the two treatment groups were tested with the use of a chi-square test with Schouten correction. Median and interquartile ranges were calculated by the Kaplan–Meier method to summarise the duration of response. Safety analyses included all the patients who had received at least one dose of a study drug. A Lan-DeMets implementation of an O'Brien-Fleming boundary function was used in the analysis of OS.
Sample size, power calculation	PFS 206 progression events was estimated to provide the study with at least 95% power to detect a hazard ratio for death or progression of disease of 0.55, with an alpha level of 0.05 (an increase in the median progression-free survival, from 6 months for vemurafenib and placebo to 11 months for vemurafenib plus cobimetinib).

Trial number (name)	CoBRIM (NCT01689519)
	OS 385 deaths will provide the study with 80% power to detect a hazard ratio for death of 0.75. Two interim analyses of OS were planned: one at the time of the final PFS analysis and the second after 256 deaths have occurred. It wa estimated 385 deaths wouldl be reached at the end of 2015.
Data management, patient withdrawals	Patients on the vemurafenib and placebo treatment arm were not eligible to cross over to the vemurafenib and cobimetinib treatment arm at disease progression and are to be followed for survival. Vemurafenib + cobimetinib 247 patients were allocated to this study arm, 246 received allocated intervention and 1 patient did not receive the allocated intervention. At the May 2014 data cut-off, 1 patient had been lost to follow-up, 104 patients had discontinued vemurafenib, 107 patients had discontinued cobimetinib, and 102 patients had discontinued both cobimetinib and vemurafenib. 247 patients were included in the analysis. Vemurafenib + placebo 248 patients were allocated to this study arm, 247 received allocated intervention and 1 patient did not receive the allocated intervention. Note that according to the database at clinical cut-off date 9th May 2014, 8 patients mistakenly received cobimetinib at least 1 cycle. At the May 2014 data cut-off, 3 patients had been lost to follow-up, 139 patients had discontinued vemurafenib, 140 patients had discontinued placebo, and 138 patients had discontinued both vemurafenib and placebo. 248 patients were included in the analysis.

OS, Overall Survival; PFS, Progression-Free Survival

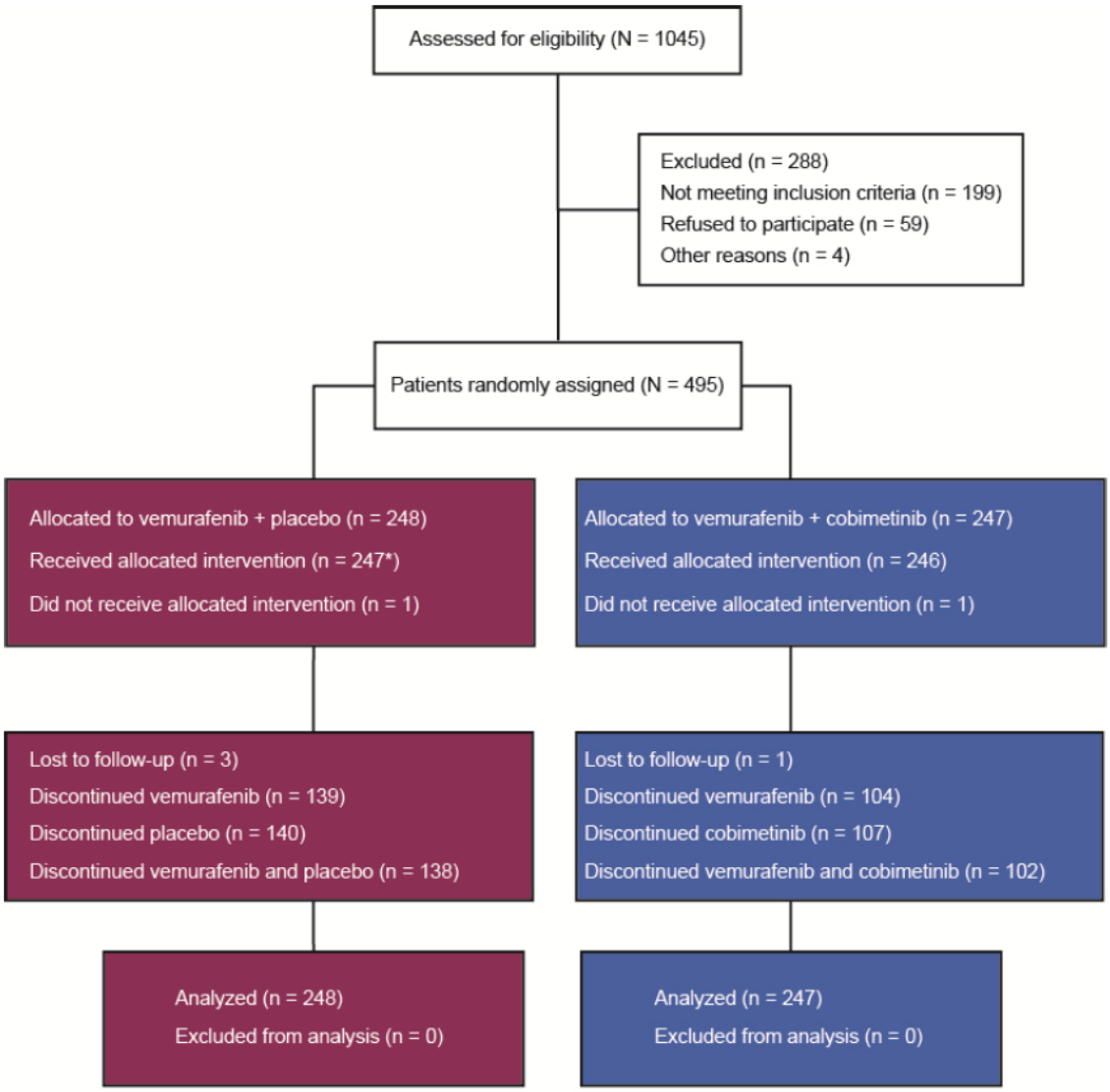
4.5 Participant flow in the relevant randomised controlled trials

4.5.1 Participants flow

A total of 1049 patients were screened, and 495 patients with BRAF V600–mutated metastatic melanoma were randomly assigned to receive vemurafenib + cobimetinib (247 patients) or vemurafenib + placebo (248) (Figure 5). The most common reason for exclusion from the study was a negative test result for the BRAF V600 mutation.

The consort diagram (Figure 5) shows the number of patients who discontinued study treatment. As of the clinical cutoff date (9 May 2014), 152 patients (59.8%) in the vemurafenib + cobimetinib arm and 101 patients (42.2%) in the vemurafenib + placebo arm were still receiving study treatment.

Figure 5 – CONSORT diagram (Larkin 2014)



*8 patients mistakenly received cobimetinib at least 1 cycle according to the database at clinical cutoff date 9 May 2104

Patients withdrawn from the study

Of the 495 randomised patients, 115 (23.2%) had withdrawn from the study at the time of the clinical cut-off for the primary efficacy analysis (9 May 2014), Table 13 (CSR). Fewer patients in the vemurafenib + cobimetinib arm (48/247, 19.4%) had discontinued from the study than in the vemurafenib + placebo arm (67/248, 27%) The most common reason for withdrawal from study was patient death (17.2%); deaths were predominantly caused by disease progression. The proportion of patients who were withdrawn for other reasons was low in both arms, most frequently withdrawal by subject. Four patients were lost to follow up.

Table 13 - Reason for withdrawal from coBRIM, ITT population (CSR)

Status n (%)	Vemurafenib + placebo (n=248)	Vemurafenib + cobimetinib (n=247)
Patients discontinued from study	67 (27)	48 (19.4)
Death	51 (20.6)	34 (13.8)
Lost to follow-up	3 (1.2)	1 (0.4)
Withdrawal by subject	13 (5.2)	10 (4.0)
Physician decision	0	3 (1.2)

4.5.2 Participant baseline characteristics.

Baseline Characteristics

The characteristics of the patients at baseline were generally well balanced between the two study groups (Table 14). Visceral metastases were present in 59% of the patients in the investigational arm and in 62% of those in the control arm. At baseline, 46% and 43% of the patients, respectively, had an elevated lactate dehydrogenase level. The median follow-up of patients at the primary efficacy analysis cutoff (9 May 2014) was 7.3 months (range, 0.5 to 16.5) (Larkin 2014).

Table 14 - Baseline Characteristics (Larkin 2014)*

Characteristic	Vemurafenib + placebo (N = 248)	Vemurafenib + cobimetinib (N = 247)
Age — years		
Median	55	56
Range	25-85	23-88
Male sex n (%)	140 (56)	146 (59)
White race n (%)†	235 (95)	227 (92)
Geographic region n (%)		
Australia, New Zealand, or Israel	38 (15)	40 (16)
Europe‡	184 (74)	182 (74)
North America	26 (10)	25 (10)
ECOG performance-status score n (%) §		
0	164/244 (67)	184/243 (76)
1	80/244 (33)	58/243 (24)
2	0/244	1/243 (<1)
Metastatic status n (%)		
Unresectable stage IIIC	13 (5)	21 (9)
M1a	40 (16)	40 (16)
M1b	42 (17)	40 (16)
M1c	152 (62)	146 (59)
Elevated LDH n (%)	104/242 (43)	112/242 (46)
History of brain metastases n (%)	2 (1)	1 (<1)
BRAF-mutation genotype n (%)‖		
V600E	174 (70)	170 (69)

V600K Could not be evaluated	32 (13) 42 (17)	24 (10) 52 (21)

*There were no significant differences in baseline characteristics between the study groups. LDH denotes lactate dehydrogenase
†Race was determined by the investigator
‡The data for patients from Russia and Turkey were included with those for Europe
§An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 indicates that the patient is fully active and able to carry on all performance without restriction and a score of 1 that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. One patient randomly assigned to receive vemurafenib and cobimetinib had an ECOG performance-status score of 1 at randomisation but had an ECOG performance-status score of 2 (indicating the patient is ambulatory and capable of all self-care but is unable to carry out any work activities and is out of bed more than 50% of waking hours) after randomisation but before the first dose was received
‖After randomisation, tumour DNA was characterized to identify specific V600 mutations using next-generation sequencing. Cases that could not be evaluated were those in which either no tumour sample was provided or sequencing could not be performed on the tissue provided

4.6 Quality assessment of the relevant randomised controlled trials

4.6.1-4.6.2 Critical appraisal of RCT

Critical appraisal of coBRIM was performed using the format provided in the NICE submission template which adhered to the Centre for Reviews and Dissemination (CRD), University of York guidance (Centre for Reviews and Dissemination (CRD) 2008). Results are presented in Table 15. The study was of high quality based on the respective responses for each category thus indicating low risk of bias in study conduct and design.

Table 15. Quality assessment of the identified RCT

Study Question	**CoBRIM (NCT01689519)**	
	How is the Question Addressed in the Study?	**Grade (Yes/No/ Not Clear/N/A)**
Was randomisation carried out appropriately?	The protocol stated that each patient was assigned an identification number and randomised to one of the two treatment arms through use of an IxRS. Randomisation was stratified by metastatic stage (unresectable Stage IIIc, M1a, and M1b; M1c) and region (North America, Europe, Australia/New Zealand/others). A stratified, permuted, block randomisation scheme was used to obtain approximately a 1:1 ratio between the two treatment groups. The protocol did not detail how the randomisation scheme was to be generated.	Not clear
Was the concealment of treatment allocation adequate?	The protocol stated that patients were to be randomly assigned to receive vemurafenib and placebo or vemurafenib and cobimetinib through use of an IxRS. The protocol also stated that placebo tablets for cobimetinib and packaging configurations were to have physical characteristics that will not permit their identification as distinct from those of cobimetinib.	Yes

Study Question	CoBRIM (NCT01689519)	
	How is the Question Addressed in the Study?	Grade (Yes/No/ Not Clear/N/A)
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The study publication stated that there were no significant differences in baseline characteristics between the study groups. The study publication also stated that the characteristics of the patients at baseline were generally well balanced between the two study groups. Visceral metastases were present in 59% of the patients in the combination group and in 62% of those in the control group. At baseline, 46% and 43% of the patients, respectively, had an elevated lactate dehydrogenase level.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The investigator, patient, and sponsor were blinded to treatment assignment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	More patients discontinued both study drugs for any reason in the vemurafenib + placebo arm (n=138) than in the cobimetinib + vemurafenib arm (n=102). However, this was not unexpected given that cobimetinib was anticipated to extend survival.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The primary, secondary and safety outcomes were reported in the primary manuscript. Congress abstracts/presentations have reported on PROs and longer-term survival analyses as well as toxicities and safety analyses. Some exploratory biomarker analyses have been presented at congress. Pharmacokinetic outcomes were excluded from the systematic review.	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The publication stated that all the efficacy analyses were carried out in the intention-to-treat population. The protocol stated that data from patients who have not experienced disease progression or death will be censored at the last tumour assessment date, and that data from patients with no post-baseline tumour assessment will be censored at the randomisation date.	Yes

IxRS, Interactive Response System; NA, Not Applicable; PRO. Patient-reported Outcome; SAE, Serious Adverse Event

4.6.3 If there is more than 1 RCT, tabulate a summary of the responses applied to each of the quality assessment criteria.

Only one RCT was identified.

*4.6.4 The complete quality assessment for each RCT should be included in an **appendix**.*

Only one RCT was identified, the quality assessment for which is provided above.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

4.7.1 Data from intention-to-treat analyses should be presented whenever possible and a definition of the included participants provided. If participants have been excluded from the analysis, the rationale for this should be given.

Data from the intention-to-treat analysis is provided under section 4.7.3 below.

4.7.2 Kaplan–Meier plots.

Kaplan-Meier plots for PFS and OS are provided under section 4.7.3 below.

4.7.3 Study clinical outcomes:

The primary analysis took place with a clinical data cutoff of 9 May 2014. The information for this cutoff is presented below and is sourced from the coBRIM publication (Larkin 2014) or the CSR. A further safety analysis of the data was conducted to support the US NDA and was published at the SMR congress 2014 (and is presented in section 4.12). An exploratory analysis of the data took place, at the request of the EU assessors, one year after enrollment of the last patient (clinical data cutoff of January 16 2015). The presented information for this data cut is sourced from the Larkin ASCO 2015 presentation. The final analysis of OS was performed with a clinical cutoff of 28 August 2015 and presented at SMR 2015.

Primary Endpoint

The study met its primary endpoint.

At the time of the primary analysis (9 May 2014), the median follow-up was 7.3 months (range, 0.5 - 16.5 months) Table 16. The combination of vemurafenib + cobimetinib significantly prolonged PFS according to investigator assessment in the ITT population: a median of 9.9 months (95% CI, 9.0 to not reached), as compared with 6.2 months (95% CI, 5.6 to 7.4) in patients treated with vemurafenib and placebo. The hazard ratio for death or progression of disease was 0.51 (95% CI, 0.39 to 0.68; p<0.001). The benefit for progression-free survival was evident in all the

pre-specified patient subgroups and according to analysis by independent radiology central review (Larkin 2014) (see Section 4.8).

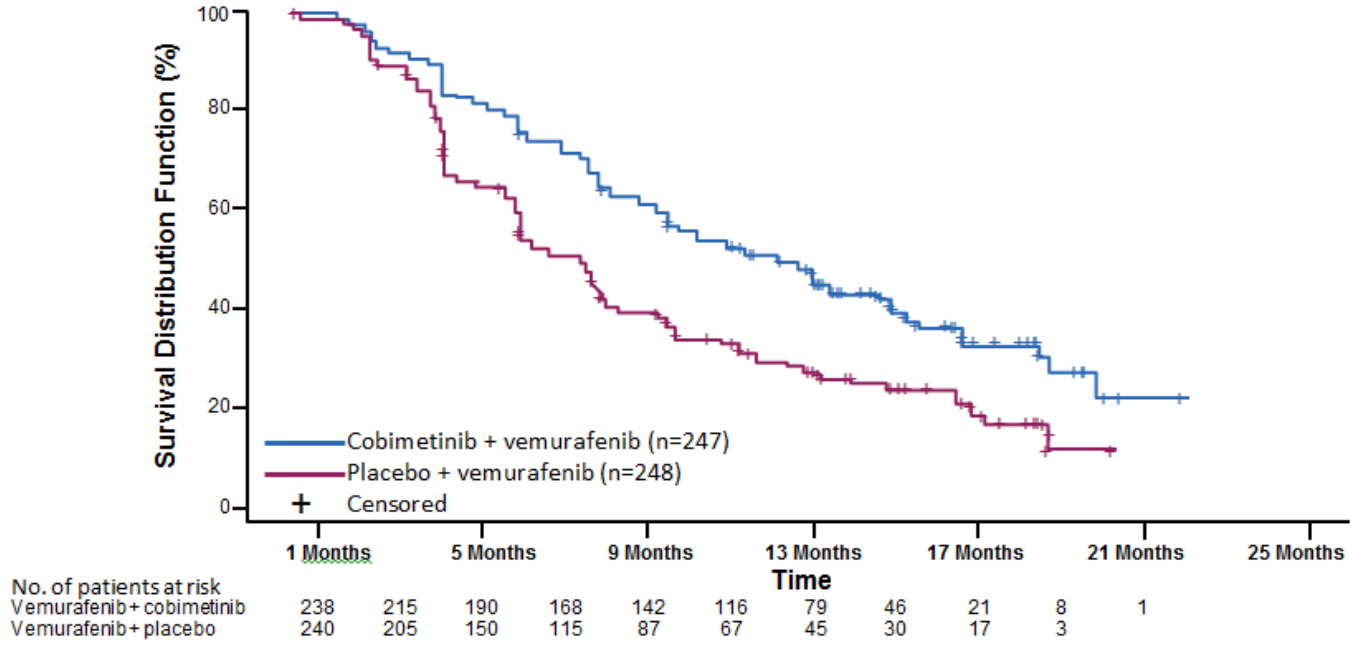
At the updated analysis (January 2015), the median follow-up was 14.2 months (range 0.5 - 24.8 months). The PFS results were consistent with the primary analysis; median PFS for vemurafenib + cobimetinib was 12.3 months (95% CI, 9.46 to 13.37) compared with 7.2 months (95% CI, 5.6 to 7.5) in patients treated with vemurafenib + placebo; HR 0.58 (95% CI, 0.46 to 0.72). Results are presented in Table 16 and Figure 6. (Larkin 2015)

Table 16 – Primary and updated analyses of PFS by investigator assessment and primary analysis of PFS by independent review (Larkin 2014, Larkin 2015)

End point	Vemurafenib and placebo (n=248)	Cobimetinib and vemurafenib (n=247)
Primary Outcome		
Data cutoff: 9 May 2014		
PFS according to investigator assessment *		
Median follow-up, months	7.3	7.3
Median duration, months (95% CI)	6.2 (5.6–7.4)	9.9 (9.0–NR)
Hazard ratio for death or disease progression (95% CI)	Reference	0.51 (0.39–0.68)
P value	Reference	<0.001
Data cutoff: 16 January 2015		
PFS according to investigator assessment		
Median follow-up, months	13.6	14.9
PFS events, n (%)	180 (72.6)	143 (57.9)
Median duration, months (95% CI)	7.2 (5.6–7.5)	12.3 (9.5–13.4)
Hazard ratio for death or disease progression (95% CI)	Reference	0.58 (0.46–0.72)
Secondary Outcome		
Data cutoff: 9 May 2014		
PFS according to assessment by independent review facility		
Median duration, months (95% CI)	6.0 (5.6–7.5)	11.3 (8.5–NR)
Hazard ratio for death or disease progression (95% CI)	Reference	0.60 (0.45–0.79)
P value	Reference	<0.001

* Patients were stratified according to geographic region and metastasis classification

Figure 6 - Kaplan-Meier Plot for PFS: Intent-to-treat population, data cutoff 16 Jan 2015 (Larkin 2015)



Secondary Endpoints

Under a nominal significance level α = 0.05 (two-sided), significant improvements were observed in all of the secondary efficacy endpoints.

Overall Survival (OS)

The information presented in Table 17 is taken from the primary analysis (cutoff date 9 May 2014), the second interim analysis of OS (cutoff date 16 Jan 2015) and the final analysis (cutoff date 28 Aug 2015).

Table 17 – Interim and final analyses of OS (Larkin 2014, draft SmPC)

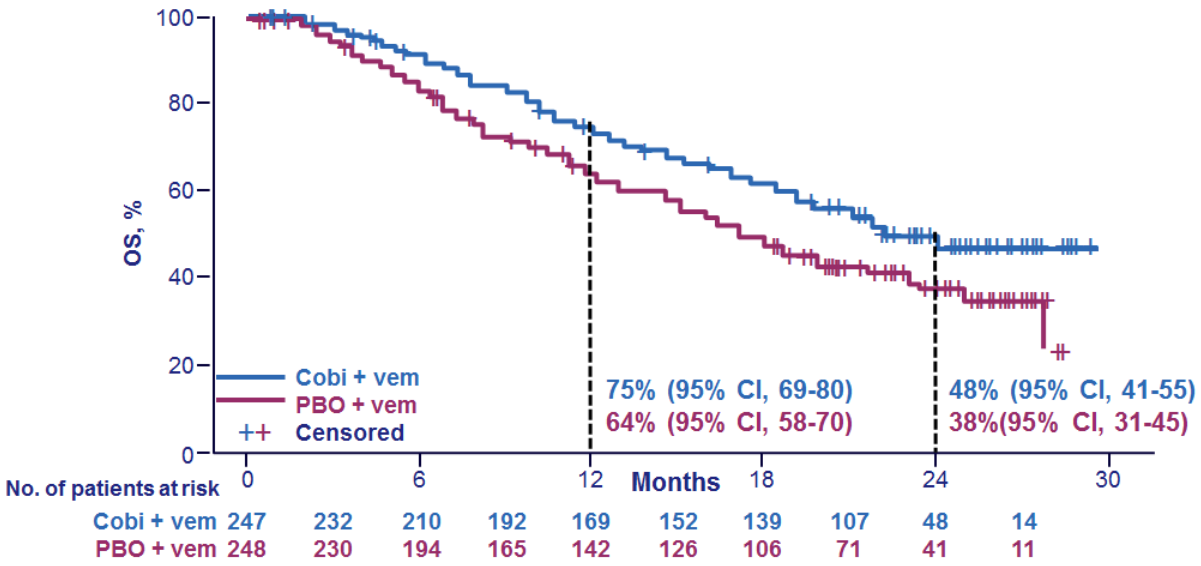
End Point	Vemurafenib + placebo n = 247	Vemurafenib + cobimetinib n = 247
Data cutoff: 9 May 2014		
Overall survival *		
Overall survival at 9 months, % (95% CI)	73 (65-80)	81 (75-87)
Median duration, months (95% CI)	NR	NR
Hazard ratio for death (95% CI)	Reference	0.65 (0.42–1.00)
p value	Reference	0.046
Data cutoff: 16 January 2015		
Overall survival *		
Median duration, months (95% CI)	NE (15.0–NE)	NE (20.7-NE)

Hazard ratio for death (95% CI)	Reference	0.65 (0.49-0.87)
Data cutoff: 28 August 2015		
Overall survival *		
Median duration, months (95% CI)	17.4 (15.0-19.8)	22.3 (20.3-NE)
Hazard ratio for death (95% CI)	Reference	0.70 (0.55-0.90)
p value	Reference	p=0.005

NE = not evaluable; NR = not reached;
* Patients were stratified according to geographic region and metastasis classification

The final protocol-specified OS analysis (data cutoff 28 Aug 2015) demonstrated that patients on vemurafenib + cobimetinib achieved 22.3 months median OS (95% CI: 20.3-not reached) versus 17.4 mo (95% CI: 15.0-19.8) (HR: 0.70; 95% CI: 0.55-0.90, *P*=0.005) for patients receiving vemurafenib + placebo, Figure 7. The benefit for OS was evident in all the pre-specified patient subgroups.

Figure 7 - Kaplan-Meier estimates of OS in the ITT population, data cutoff 28 Aug 2015 (Atkinson 2015)



Response rates

At the time of the primary analysis (9 May 2014), the response rate was significantly higher in the vemurafenib + cobimetinib group than in the control group (Table 18) (Larkin 2014). Overall, 68% of patients in the vemurafenib + cobimetinib group had an objective response, as compared with 45% in the control group (p<0.001).The

rate of complete response was also significantly higher in the combination group than in the control group (10% vs. 4%). The majority of responses were seen by the time of the first tumour assessment at 8 weeks. The median duration of response was 7.3 months in the control group, and the median was not reached in the vemurafenib + cobimetinib group.

At the updated analysis (16 Jan 2015) a total of 172 patients treated with vemurafenib + cobimetinib attained an objective response, corresponding to a confirmed ORR of 69.6% (95% CI: 63.5% to 75.3%). Approximately 16% of patients in the vemurafenib + cobimetinib group attained a complete response, Table 18. For the 172 responders in the vemurafenib + cobimetinib arm, the median duration of response was 13.0 months (95% CI 11.1 to 16.6). For the 124 responders in the vemurafenib + placebo arm, the median duration of response was 9.2 months (95% CI 7.5 to 12.8), Table 18 (Larkin 2015).

Table 18 - Primary and updated analyses of best objective response rate and duration of response, (Larkin 2014, Larkin 2015)

End point	Vemurafenib + placebo n = 248	Vemurafenib + cobimetinib n = 247
Data cutoff: 9 May 2014		
Complete response Partial response Stable disease Progressive disease No complete response or progressive disease Could not be evaluated **	11 (4) 100 (40) 105 (42) 25 (10) 1 (<1) 6 (2)	25 (10) 142 (57) 49 (20) 19 (8) 0 12 (5)
Complete or partial response No. of patients Percent of patients (95% CI) P value	 111 45 (38–51) Reference	 167 68 (61–73) <0.001
Median duration of response, months (95% CI)	7.3 (5.8–NR)	NR (9.3–NR)
Data cutoff: 16 Jan 2015		
Complete response Partial response	26 (11) 98 (40)	39 (16) 133 (54)
ORR (complete or partial response) No. of patients Percent of patients (95% CI)	 124 50.0 (43.61-56.39)	 172 69.6 (63.49-75.31)

Difference in ORR, % (95% CI)	Reference	19.64 (10.95-28.32)
Duration of response (DOR) Patients with event, n (%) Median DOR, months (95% CI) Range	 73 (58.9) 9.23 (7.52-12.78) 1.77-17.68	 84 (48.8) 12.98 (11.10-16.62) 2.86-20.11

Quality of life

The PRO measures were the EORTC QLQ-C30 and the EQ-5D-5L.

HRQoL, disease- and treatment-related symptoms, and functional impact were assessed using the EORTC QLQ-C30 at baseline, Days 1 and 15 in Cycles 1 and 2, (C1D1; C1D15; C2D1; C2D15 respectively) and every other cycle thereafter until patient withdrawal or end of study. Data were evaluable until Cycle 8 Day 1 (C8D1), after which too few patients remained enrolled in the vemurafenib + placebo treatment arm to allow for meaningful conclusions (<25% from baseline) (Dreno 2015).

Completion rates of the EORTC QLQ-C30 were above 99% at baseline and remained high (>88%) for all assessments. Across all functioning domains (cognitive, emotional, social, role, and physical), and most symptoms (appetite loss, constipation, nausea and vomiting, dyspnoea, pain, fatigue) of the EORTC QLQ-C30, patients in the vemurafenib + cobimetinib arm reported better scores at all or most of the post-baseline time points evaluated, as compared to those in the vemurafenib + placebo arm. However, the differences from baseline in function and symptoms did not constitute a clinically meaningful change (≥ 10 point increase or decrease from baseline), indicating comparable quality of life by treatment arm.

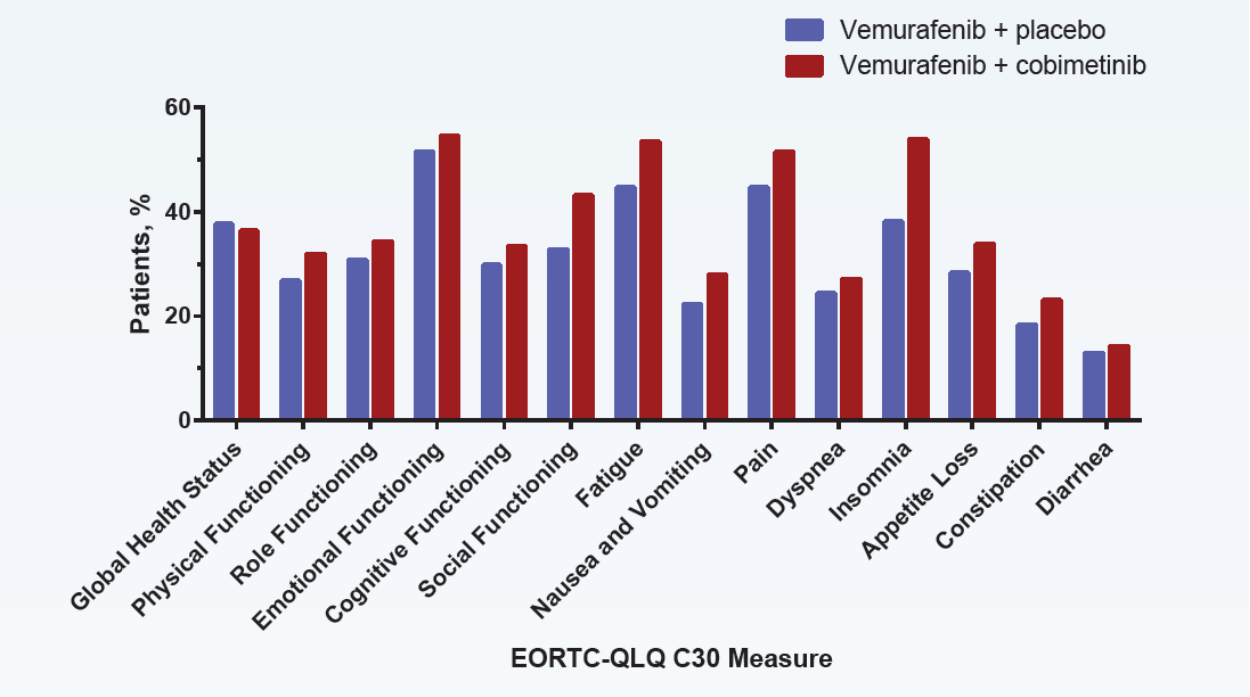
Patients in the vemurafenib + cobimetinib arm experienced clinically meaningful improvement in insomnia (C2D15, C4D1, C6D1, C8D11), whereas, patients in the vemurafenib + placebo arm did not show a clinically meaningful change from baseline in insomnia. Patients in the vemurafenib + cobimetinib arm experienced clinically meaningful worsening of diarrhoea from baseline at C1D15 and C2D15 but not in subsequent cycles; no clinically meaningful change from baseline for diarrhoea was observed in the vemurafenib + placebo arm.

Exploratory analysis

An exploratory analysis was performed, in which patients were considered to have had a clinically meaningful improvement in EORTC QLQ-C30 score if they had at least a 10-point improvement in the score at one or more post-baseline assessments.

For global health status, as well as most functioning and symptom scales, the difference in proportion of responders was approximately < 5%, indicating similarity in HRQoL between the two treatment arms. Larger differences were seen for insomnia (16%) and social functioning (11%), and to a lesser extent, fatigue (9%), and pain (7%); Figure 8 (Dreno 2015).

Figure 8 - Proportions of patients with clinically meaningful improvement in EORTC QLQ-C30 (Dreno 2015)



Summary of QoL data

The EORTC QLQ-C30 questionnaire is completed by all patients until withdrawal or completion of the study. Only a small proportion of patients who discontinued any study treatment completed the EORTC QLQ-C30 questionnaire at follow-up visits (12.8% of patients in the vemurafenib + cobimetinib arm and 12.4% of patients in the vemurafenib + placebo arm, at week 4) (CSR). 35.5% of patients in the vemurafenib

+ cobimetinib arm and 47% of patients in the vemurafenib + placebo arm discontinued study treatment because of disease progression. Since few patients completed the EORTC QLQ-C30 questionnaire upon discontinuation of study treatment, the impact on HRQoL post disease progression is not captured. The increase in PFS associated with vemurafenib + cobimetinib compared to vemurafenib + placebo arm may impact HRQoL. However this cannot be fully elucidated with the EORTC QLQ-C30 questionnaire as it was not generally employed post disease progression in either arm of the study. In summary, the data reflects the quality of life of trial recruits who are progression-free and does not clearly reflect the likely quality of life benefits of the more effective combination therapy in keeping more patients progression-free for longer

4.8 Subgroup analysis

4.8.1 Provide details of any subgroup analyses carried out.

Subgroup analyses were pre-planned for the study (CSR). The treatment effect of cobimetinib in combination with vemurafenib on PFS and OS was examined in subgroups defined by demographic and baseline characteristics and stratification factors to assess consistency. Because some subgroups could have small sample sizes, these analyses were considered exploratory. These subgroup analyses are presented below for the updated PFS analysis (January 2015 data cut) and final OS analysis (August 2015 data cut).

4.8.2 Clearly specify the characteristics of the participants in the subgroups and explain the appropriateness of the analysis to the decision problem.

The subgroups included the following:

- Disease stage (IIIc, M1a, M1b, M1c)
- Disease stage (IIIc/M1a/M1b, M1c)
- Age (≤ 65 years, > 65 years) at randomisation
- Race (non-White, White)
- Sex (female, male)
- Geographic region (North America, Europe, Australia/New Zealand/others)

• Eastern Cooperative Oncology Group performance status at randomisation (0, 1)
• LDH (normal, elevated)
• Presence of brain metastases (yes, no)
• Time since metastatic disease diagnosis (< 6 months, ≥ 6 months)
• Prior adjuvant therapy (Yes, No)
• BRAF V600 mutation status (V600E, V600K)

The analyses were conducted to assess consistency of the results according to prognostic factors as well as age, race and geographical location

4.8.3 Provide details of the statistical tests used in the primary analysis of the subgroups, including any tests for interaction.

For PFS, the Kaplan-Meier estimated median time to event was summarised by treatment arm for each of the subgroups defined above, as well as with an HR (treatment:control) estimated by unstratified Cox regression, which was displayed as a Forest plot.

4.8.4 Provide a summary of the results for the subgroups

Overall, the results of the subgroup analyses of investigator-assessed PFS and OS were consistent with the results seen in the overall ITT population (Figure 9 and Figure 10 below). In all subgroups the point estimates for the PFS hazard ratios were below 1 favouring cobimetinib + vemurafenib versus placebo + vemurafenib and similar to the value for the whole trial population. (Larkin 2014)

For some subgroups the upper limit of the 95% confidence interval was above 1. However, it is of note that in some of these subgroups the number of patients is low, and the study was not powered to show significance within subgroups, therefore the subgroup results – particularly in these smaller subgroups – should be interpreted with caution. (Larkin 2015).

Figure 9 - Forest plot to show subgroup analyses of PFS, data cutoff 16 Jan 2015 (Larkin 2015)

Baseline Risk Factors	Total n	Placebo + vemurafenib (n=248) n	Events	Median (months)	Cobimetinib + vemurafenib (n=247) n	Events	Median (Months)	Hazard Ratio	95%Wald CI
All Patients	495	248	180	7.2	247	143	12.3	0.59	(0.47, 0.73)
Disease Stage (IIIc/M1a/M1b, or M1c)									
M1C	299	153	128	5.5	146	94	9.5	0.52	(0.40, 0.68)
Unresectable Stage IIIC/M1A/M1B	196	95	52	11.0	101	49	13.4	0.73	(0.49, 1.08)
Age Group (yr)									
< 65	362	179	128	7.2	183	107	12.6	0.61	(0.47, 0.79)
≥ 65	133	69	52	5.6	64	36	11.2	0.52	(0.34, 0.80)
Sex									
Female	209	108	72	7.5	101	52	12.9	0.57	(0.40, 0.82)
Male	286	140	108	5.7	146	91	11.1	0.58	(0.44, 0.77)
Geographic Region									
Australia/New Zealand/Others	78	38	26	7.4	40	20	13.3	0.57	(0.32, 1.03)
Europe	366	184	138	6.0	182	107	11.2	0.58	(0.45, 0.75)
N. America	51	26	16	7.5	25	16	11.2	0.57	(0.28, 1.17)
ECOG Performance Status									
0	348	164	110	7.6	184	100	12.9	0.65	(0.49, 0.85)
1	138	80	66	5.5	58	41	10.0	0.53	(0.35, 0.78)
Screening Serum LDH									
Elevated	216	104	85	5.4	112	78	8.2	0.57	(0.42, 0.78)
Normal	268	138	90	7.8	130	65	13.4	0.59	(0.43, 0.81)
Prior Adjuvant Therapy									
Yes	48	24	16	7.2	24	12	16.5	0.60	(0.28, 1.27)
No	447	224	164	7.2	223	131	11.2	0.59	(0.47, 0.74)
$BRAF^{V600}$ Mutation Status									
V600E	344	174	126	7.2	170	102	10.6	0.64	(0.49, 0.83)
V600K	56	32	24	6.0	24	14	12.4	0.52	(0.27, 1.02)

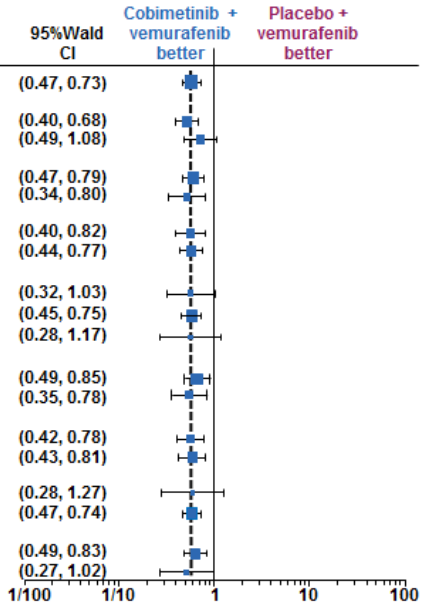
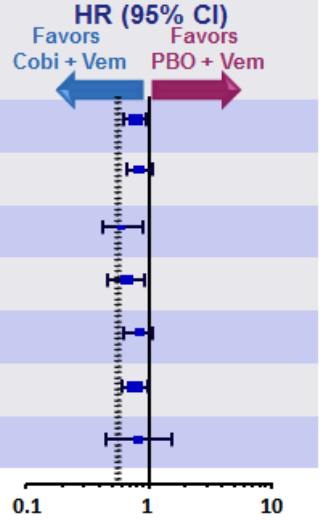


Figure 10 Forest plot to show subgroup analyses of OS, data cutoff August 2015 (Atkinson 2015)

	n		PFS
	PBO + Vem	Cobi + Vem	Median Cobi + Vem vs PBO + Vem
All patients	248	247	22.3 vs 17.4
ECOG PS 0	164	184	23.8 vs 19.8
ECOG PS 1	80	58	21.8 vs 11.7
LDH level normal	138	130	NE vs 23.3
LDH ≥ ULN	104	112	14.8 vs 11.2
V600E	174	170	21.9 vs 17.5
V600K	32	24	24.1 vs 16.7



NE, not evaluable; ULN, upper limit of normal.

4.9 Meta-analysis

A meta-analysis was not considered necessary. The systematic literature review identified one relevant clinical trial, the coBRIM study. This study directly compares the intervention to one of the comparators listed in the final scope.

4.10 Indirect and mixed treatment comparisons

4.10.1 Search strategies to identify trials included in the indirect comparison and network meta-analyses.

The systematic literature review of the comparators listed in the final scope was conducted on 7th April 2015. Details of the search criteria, information sources, strategy, and results are available in appendix 4.

Study selection

4.10.2 Details of the treatments to be compared.

The final scope for this appraisal includes two comparators: the BRAF inhibitors vemurafenib and dabrafenib, as monotherapy treatments. The coBRIM study includes a direct comparison to vemurafenib, but does not include a treatment arm with dabrafenib. Thus an indirect treatment comparison is required to appraise the clinical- and cost-effectiveness of cobimetinib + vemurafenib to dabrafenib monotherapy treatment.

The NMA was conducted to support pricing and reimbursement submissions across all markets, and included comparators not listed in the final scope (immunotherapies, DCIT and trametinib). The NMA included a scenario which restricted the evidence base to only include those studies reporting on patients who were BRAF mutation positive (i.e. no inclusion of patients with wild-type status). This scenario was considered most appropriate for the appraisal scope, and is the focus of discussion below. This scenario produced a small but connected network, which allowed comparison between cobimetinib + vemurafenib and dabrafenib.

As this restricted network is taken from the broader NMA, the methods of the latter are described below, and results focus on the analysis which falls within the appraisal scope.

4.10.3 Search inclusion and exclusion selection criteria

A systematic literature review was conducted to identify relevant clinical trials. Full details are available in Appendix 4. The inclusion and exclusion criteria applied during the systematic literature review are found below in Table 19.

Table 19 Criteria used in the trial selection process

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Rationale
Population	Treatment naïve adults with metastatic or unresectable stage IIIC and/or stage IV melanoma. Studies enrolling patients who had received prior treatment for an earlier stage of the disease, but who were treatment naïve when presenting with metastatic disease were eligible for inclusion.	Studies with mixed population for which results for metastatic or unresectable melanoma patients were not reported separately, at least 80% of the enrolled patients were required to have unresectable or metastatic melanoma	Alignment with marketing authorisation and appraisal scope

Intervention and comparator	Cobimetinib in combination with vemurafenib
	• Targeted drugs
	  ○ Cobimetinib
	  ○ Dabrafenib
	  ○ Trametinib
	  ○ Vemurafenib
	• Immunotherapy
	  ○ Interferon
	  ○ Ipilimumab
	  ○ Nivolumab
	  ○ Pembrolizumab
	• Chemotherapy
	  ○ Cisplatin
	  ○ Dacarbazine
	  ○ Fotemustine
	  ○ Temozolomide
	• Placebo
		Studies with any other treatments	The NMA was conducted to support pricing and reimbursement submissions across all markets. Results focus on a restricted netwok which assesses the within-scope comparators

Outcomes	The primary outcomes of interest were:
	• Efficacy:
	  ○ OS
	  ○ 1 year survival rate
	  ○ PFS
	  ○ TTP
	  ○ Response rates (complete response, partial response, stable disease, progressive disease)
	• Safety:
		Studies not reporting any of the included outcomes	Alignment with appraisal scope

	○ All grade 3/4 AEs • HRQoL		
Trial design	RCTs: Any design and all phases	Non-randomised studies	Allow inclusion into network
Language restrictions	English: English abstracts of foreign publications were considered	Papers without abstracts available in English	Usability of publication

4.10.4 Summary of trials used to carry out the indirect comparison

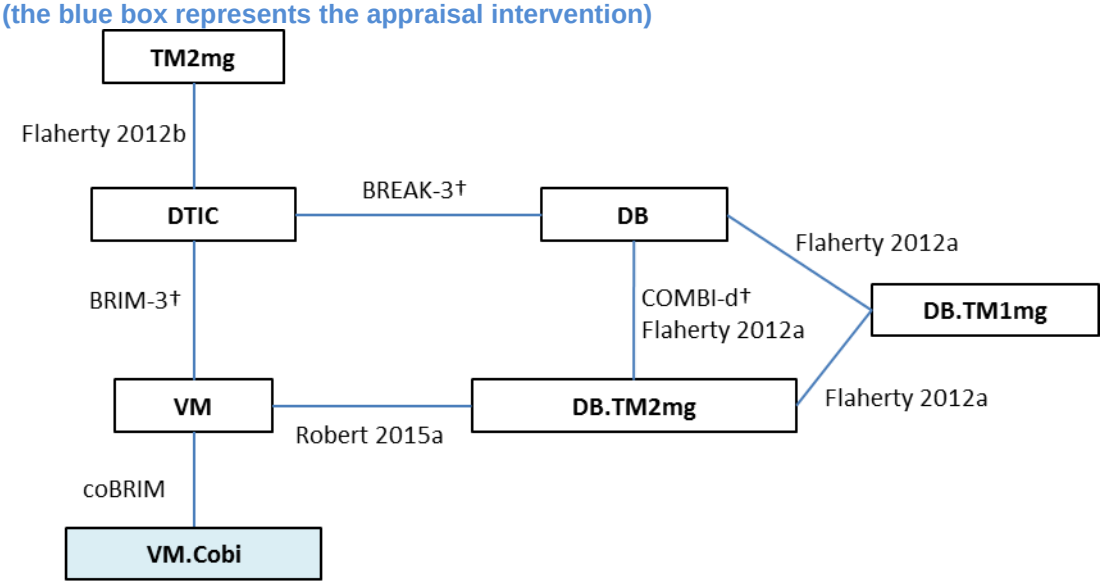
Following the systematic literature review, 29 unique trials were identified (details appendix 4) from 35 publications. A feasibility assessment was conducted and five scenarios were considered clinically appropriate to assess the evidence for first-line treatment of metastatic or unresectable malignant melanoma.

One of these scenarios restricted the evidence base to those studies reporting patients who were BRAF mutation positive (i.e. no inclusion of patients with wild-type status). As described above, this scenario was considered most appropriate for the appraisal scope. The diagram of this restricted network is shown in Figure 11 below, and the included studies are listed in Table 20.

Table 20 Summary of the trials used to carry out the indirect or mixed treatment comparison

References of trial	Intervention A	Intervention B	Intervention C
coBRIM (Larkin, 2014)	Cobimetinib + vemurafenib	Vemurafenib	
BRIM-3 (Chapman 2011; Chapman 2012; McArthur 2014)	Vemurafenib	Dacarbazine	
Flaherty 2012a	Trametinib 1mg + dabrafenib	Trametinib 2mg + dabrafenib	Dabrafenib
Flaherty 2012b	Trametinib 2mg	Chemotherapy (dacarbazine or paclitaxel)	
BREAK-3 (Hauschild 2012; Hauschild 2013)	Dabrafenib	Dacarbazine	
COMBI-d (Long 2014; Long 2015)	Trametinib 2mg + dabrafenib	Dabrafenib	
COMBI-v (Roberts 2015)	Trametinib 2mg + dabrafenib	vemurafenib	

Figure 11 Network of evidence for OS and PFS in studies for BRAF mutation positive patients (the blue box represents the appraisal intervention)



TM2mg = trametinib 2mg; DTIC = dacarbazine, DB = dabrafenib, VM = vemurafenib, DB.TM2mg = dabrafenib + trametinib 2mg; DB.TM1mg = dabrafenib + trametinib 1mg; VM.Cobi = vemurafenib + cobimetinib

4.10.5 *If the table or network diagram provided in response to section 4.10.4 does not include all the trials that were identified in the search strategy, the rationale for exclusion should be provided.*

Please see 4.10.4.

Methods and outcomes of included studies

4.10.6 Provide the rationale for the choice of outcome measure chosen, along with the rationale for the choice of outcome scale selected.

Outcome measures of particular interest for the NMA were PFS and OS. These outcomes are consistent with the appraisal scope, and either PFS or OS was the primary efficacy endpoint for all included studies in Table 20. These outcomes are also highly relevant to the condition under appraisal as discussed in section 3.

4.10.7 Discuss the populations in the included trials

The full trial populations in the included studies (Table 20) are consistent with the appraisal scope: 'Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma'. These studies did not include any patients inconsistent with the appraisal scope, therefore no sub-group analysis was required.

4.10.8 Apparent or potential differences in patient populations between the trials..

The patients recruited into studies listed in Table 20 are consistent between trials, and with the appraisal scope. Baseline characteristics can be found in appendix 5, and are broadly consistent between trials.

4.10.9 Study methods, outcomes and patient baseline characteristics

Please refer to appendix 6

Risk of bias

4.10.10 In an appendix, provide a complete quality assessment of each trial included in response to section 4.10.4.

Please refer to appendix 6.

4.10.11 Identify any risk of bias within the trials identified, and describe any adjustments made to the analysis.

Risk of bias was assessed using the Cochrane Risk of Bias Tool. After removal of studies with a high risk of bias according to the tool, only McArthur et al, 2014 and Larkin et al, 2014 were includable. Limiting the network to only these studies would not have allowed comparisons to be made.

Methods of analysis and presentation of results

4.10.12 Indirect treatment comparison methodology.

As described in section 4.10.4, a feasibility assessment identified five possible scenarios, with one of these scenarios appropriate to the appraisal scope.

Model Overview:

The NMA estimates average treatment effects (outcomes of interest: OS and PFS) for all possible comparisons included in the network. The NMA was conducted under a Bayesian framework.

The evidence base included one closed loop allowing assessment of consistency (see 4.10.19).

The model was fitted using Markov Chain Monte Carlo (MCMC) estimator as implemented in the just another Gibbs sampler (JAGS) software. The model was run for 70,000 burn-in simulations, using three chains, and parameters were monitored over a further 70,000 simulations.

The following addressed diagnosis of the convergence:

- Visual inspection of the trace plots to check if the simulations of the three chains overlap for the monitored parameters
- Density plots of the treatment effects
- Gelman and Rubin's convergence diagnostic statistic of <1.05, which is widely accepted as the level for implying convergence (Brooks 1998).

Treatment Effect Scales

NMAs were conducted for the outcomes OS and PFS on two scales; proportional hazards (PH) and accelerated failure time (AFT). Evidence from a previously conducted NMA (Bexelius 2014) found the AFT survival model was a better fit compared with the PH model, for trials in metastatic melanoma. Diagnostics plots were used to assess this assumption and can be found in appendix 6.

Based on the previous NMA (Bexelius 2014) and the diagnostic results of this analysis, the AFT model appears to fit the data more appropriately for the individual studies compared with PH assumption. Therefore, the AFT scale has been utilised with results presented below.

Recreating individual patient data to estimate acceleration factor

As the acceleration factor was not routinely reported in trials included in the NMA, it was necessary to recreate individual patient data so that survival models could be fitted and test statistics for each publication estimated. Details of the methodology and results can be found in appendix 7.

Key assumptions in NMA

The main assumption in the NMA is the treatment node of dacarbazine or paclitaxel in the Flaherty 2012 trial is considered to interact in the same way as dacarbazine in the other trials.

4.10.13 Supply any programming language in an appendix (for example the WinBUGS code).

Please see appendix 8

4.10.14-4.10.16 Results of the analysis and heterogeneity assessment

Results of the NMA in Figure 11 are presented as the inverse AFT, comparing treatment A with treatment B.

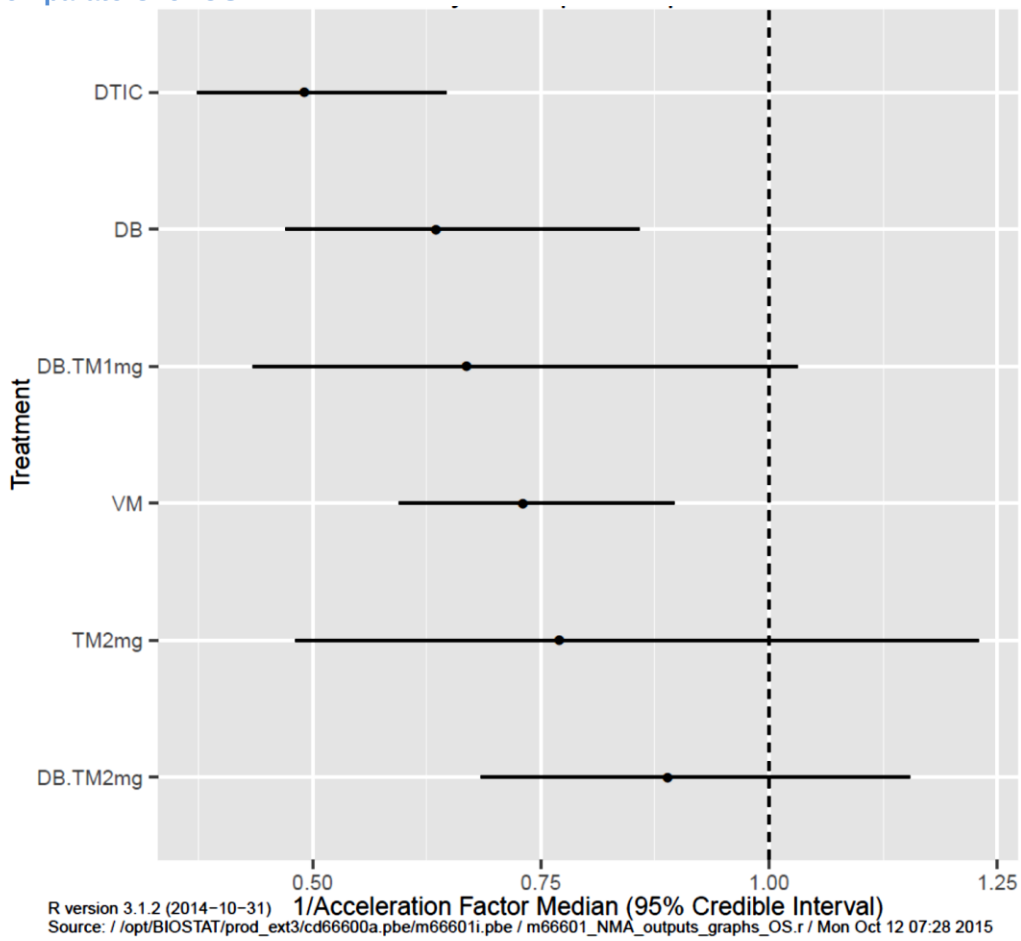
Overall Survival

Results for OS are presented in Table 21 with a forest plot of cobimetinib + vemurafenib versus other treatment nodes in Figure 12

Table 21 NMA results reporting 1/AFT (95% CI) for OS

Treatment A	Treatment B						
	DTIC	DB.TM1mg	DB.TM2mg	DB	TM2mg	VM	VM.Cobi
DTIC		1.36 (0.91, 2.03)	1.81 (1.45, 2.26)	1.29 (1.02, 1.64)	1.57 (1.07, 2.29)	1.49 (1.24, 1.79)	2.04 (1.55, 2.68)
DB.TM1mg	0.73 (0.49, 1.09)		1.33 (0.94, 1.89)	0.95 (0.67, 1.34)	1.15 (0.66, 2.00)	1.09 (0.75, 1.60)	1.50 (0.97, 2.30)
DB.TM2mg	0.55 (0.44, 0.69)	0.75 (0.53, 1.07)		**0.71 (0.60, 0.85)**	0.87 (0.56, 1.35)	**0.82 (0.70, 0.97)**	1.12 (0.87, 1.46)
DB	0.77 (0.61, 0.98)	1.05 (0.74, 1.49)	**1.40 (1.17, 1.67)**		1.21 (0.77, 1.90)	1.15 (0.92, 1.43)	**1.57 (1.17, 2.13)**
TM2mg	0.64 (0.44, 0.94)	0.87 (0.50, 1.51)	1.16 (0.74, 1.80)	0.83 (0.53, 1.29)		0.95 (0.62, 1.45)	1.30 (0.81, 2.08)
VM	0.67 (0.56, 0.81)	0.92 (0.63, 1.34)	**1.22 (1.04, 1.43)**	0.87 (0.70, 1.08)	1.05 (0.69, 1.61)		**1.37 (1.12, 1.68)**
VM.Cobi	0.49 (0.37, 0.65)	0.67 (0.43, 1.03)	0.89 (0.68, 1.15)	**0.63 (0.47, 0.86)**	0.77 (0.48, 1.23)	**0.73 (0.59, 0.90)**	

Figure 12 Forest plot of the treatment comparison obtained from the NMA for VM.Cobi vs comparators for OS



Abbreviations: AFT, accelerated time failure; CrI, credible interval; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg; DTIC, dacarbazine; OS, overall survival; TM2mg, trametinib 2mg; VM, vemurafenib; VM.Cobi, vemurafenib plus cobimetinib

Progression Free Survival

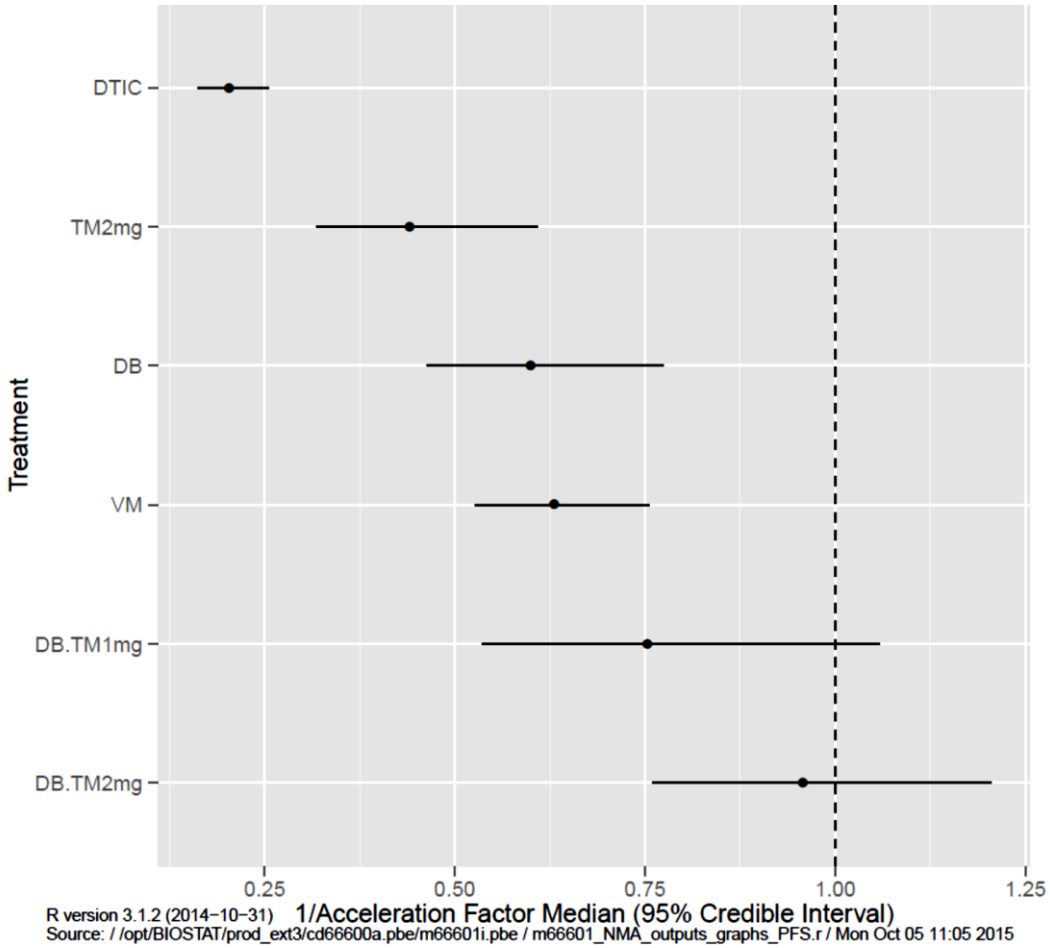
Results for PFS are presented in Table 22 with a forest plot of cobimetinib + vemurafenib versus other treatment nodes in Figure 13.

Table 22 NMA results reporting 1/AFT (95%CrI) for PFS

Treatment A	Treatment B						
	DTIC	DB.TM1mg	DB.TM2mg	DB	TM2mg	VM	VM.Cobi
DTIC		3.71 (2.76, 5.00)	4.72 (3.96, 5.62)	2.95 (2.45, 3.56)	2.17 (1.72, 2.74)	3.11 (2.71, 3.56)	4.93 (3.93, 6.18)
DB.TM1mg	0.27 (0.20, 0.36)		1.27 (0.98, 1.65)	0.80 (0.61, 1.03)	**0.58 (0.40, 0.85)**	0.84 (0.63, 1.12)	1.33 (0.95, 1.86)
DB.TM2mg	0.21 (0.18, 0.25)	0.79 (0.61, 1.02)		**0.63 (0.54, 0.73)**	**0.46 (0.34, 0.61)**	**0.66 (0.57, 0.76)**	1.04 (0.83, 1.32)

DB	0.34 (0.28, 0.41)	1.26 (0.97, 1.63)	**1.60 (1.37, 1.86)**		**0.74 (0.55, 0.99)**	1.05 (0.88, 1.26)	**1.67 (1.29, 2.16)**
TM2mg	0.46 (0.36, 0.58)	**1.71 (1.17, 2.49)**	**2.17 (1.63, 2.91)**	**1.36 (1.01, 1.83)**		**1.43 (1.09, 1.87)**	**2.27 (1.64, 3.14)**
VM	0.32 (0.28, 0.37)	1.19 (0.90, 1.59)	**1.52 (1.32, 1.75)**	0.95 (0.79, 1.14)	**0.70 (0.53, 0.91)**		**1.59 (1.32, 1.90)**
VM.Cobi	0.20 (0.16, 0.25)	0.75 (0.54, 1.06)	0.96 (0.76, 1.20)	**0.60 (0.46, 0.77)**	**0.44 (0.32, 0.61)**	**0.63 (0.53, 0.76)**	

Figure 13 Forest plot of the treatment comparison obtained from the NMA for VM.Cobi vs comparators for PFS



Abbreviations: AFT, accelerated time failure; CrI, credible interval; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg; DTIC, dacarbazine; OS, overall survival; TM2mg, trametinib 2mg; VM, vemurafenib; VM.Cobi, vemurafenib plus cobimetinib

Summary of results

Due to a lack of direct trial evidence, an indirect treatment comparison was conducted to compare the intervention (cobimetinib + vemurafenib) to the comparator, dabrafenib. To construct a network additional therapies were included,

however the results of these indirect comparisons are not required for this appraisal, and are not included in further detail.

The AFT model was determined to fit the data most appropriately (see section 4.10.2), as such results of the NMA are presented as the inverse of the acceleration factor (1/AFT).

- 1/AFT of 1 indicates there is no difference between the treatment and control
- 1/AFT < 1 favours treatment
- 1/AFT >1 favours control

OS: 1/AFT (95% CI)

Cobimetinib + vemurafenib vs. dabrafenib = 0.635 (0.47, 0.86)

PFS: 1/AFT (95% CI)

Cobimetinib + vemurafenib vs. dabrafenib = 0.599 (0.46, 0.77)

4.10.16 Provide the results of the statistical assessment of heterogeneity. The degree of heterogeneity, and the reasons for it, should be explored as fully as possible.

The NMA was performed with a fixed-effect model, thus assuming no variation in relative treatment effects across studies. Each pairwise comparison within the network included only one study. As such it was not possible to assess heterogeneity.

4.10.17 Justify the choice of random or fixed effects model.

Due to the small network and limited number of studies, a random-effects model will provide a poor estimate of the distribution of intervention effects. The model fit of the fixed- and random-effects models conducted for each outcome was compared using the deviance information criterion (DIC). The DIC values for the base case analyses of PFS and OS indicated that the fixed effects models provided improved model fit compared with the random effect models: -20.98 and -20.43 for PFS fixed effect and

random effects respectively. DIC values of -15.26 and -14.11 for OS fixed effect and random effects respectively.

4.10.18 *If there is doubt about the relevance of particular trials, present separate sensitivity analyses in which these trials are excluded.*

See section 4.10.11

4.10.19 *Heterogeneity and inconsistencies between the direct and indirect evidence on the technologies.*

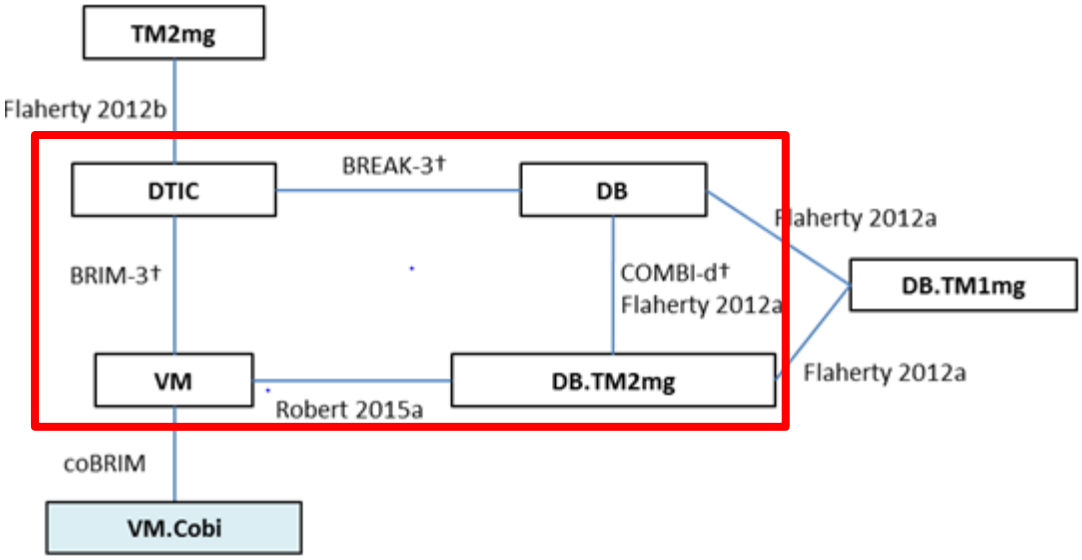
Heterogeneity between results of pairwise comparisons

Each pairwise comparison in the NMA was characterised by one study, as such it was not possible to assess heterogeneity across studies for particular pairwise comparison.

Inconsistency Assessment

The NMA included one closed loop, with four treatments as shown in Figure 14 below.

Figure 14 Closed independent loop available in network



The Bucher method was used to assess consistency by comparing direct estimate with indirect estimate. The z value to test the null hypothesis of no inconsistency was -0.67 (p=0.50), smaller than 1.96 in absolute value (using the normal

approximation with a significance level of 5%), reflecting no evidence of inconsistency. The z value for OS was set at -0.88, also showing no evidence of inconsistency.

4.11 Non-randomised and non-controlled evidence

4.11.1 Present non-randomised and non-controlled evidence

No non-randomised or non-controlled evidence was identified which was relevant to the decision problem

4.12 Adverse reactions

4.12.1-2 Adverse reactions reported in the study

Safety was an endpoint in the coBRIM trial. In light of this, no additional searches have been undertaken and no additional studies will be considered in relation to adverse reactions. An additional safety analysis will be conducted following the analysis for final OS, and is [redacted]

The data presented in this section are an overview of the cumulative safety data reported at the time of the primary data-cut (9 May 2014) for coBRIM. A further safety analysis of the data was conducted to support the US NDA (data cutoff 19 Sep 2014) and was published at the SMR congress 2014 (Dreno 2014) and ASCO 2015 (de la Cruz-Merino 2015). Data from this safety analysis are also included in this section. Results of the most recent safety analysis conducted at the final OS assessment (August 2015) are not yet available.

A total of 493 patients (>99%) received at least one dose of study drug and were included in the safety analysis (Larkin 2014). The median follow-up for all patients was 7.3 months (Dreno 2014). Adverse events that were reported in at least 20% of patients in either group are shown in Table 23.

Table 23 - Common adverse events* (Larkin 2014)

Adverse event	Vemurafenib and placebo (n=239)				Vemurafenib and cobimetinib (n=254)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
	Number of patients (%)							
Any adverse event	21 (9)	70 (29)	117 (49)	22 (9)	19 (7)	66 (26)	125 (49)	34 (13)
Most common adverse events†								
Diarrhoea	51 (21)	16 (7)	0	0	99 (39)	29 (11)	16 (6)	0
Nausea	43 (18)	12 (5)	2 (1)	0	75 (30)	22 (9)	2 (1)	0
Vomiting	21 (9)	6 (3)	2 (1)	0	41 (16)	10 (4)	3 (1)	0
Rash	46 (19)	27 (11)	12 (5)	0	55 (22)	29 (11)	13 (5)	2 (1)
Photosensitivity reactions	25 (10)	12 (5)	0	0	48 (19)	18 (7)	6 (2)	0
Hyperkeratosis	49 (21)	14 (6)	5 (2)	0	23 (9)	3 (1)	0	0
Fatigue	42 (18)	24 (10)	7 (3)	0	48 (19)	24 (9)	9 (4)	0
Pyrexia	43 (18)	10 (4)	0	0	49 (19)	13 (5)	4 (2)	0
Arthralgia	53 (22)	31 (13)	12 (5)	0	54 (21)	23 (9)	6 (2)	0
Alopecia	55 (23)	14 (6)	1 (<1)	0	33 (13)	1 (<1)	1 (<1)	0
Increased alanine amino-transferase	17 (7)	11 (5)	14 (6)	1 (<1)	16 (6)	15 (6)	28 (11)	1 (<1)
Increased aspartate amino-transferase	15 (6)	10 (4)	4 (2)	1 (<1)	17 (7)	18 (7)	21 (8)	0
Increased creatine kinase	6 (3)	1 (<1)	0	0	23 (9)	27 (11)	17 (7)	9 (4)
Selected adverse events								
Cutaneous squamous-cell carcinoma	0	0	27 (11)	0	0	1 (<1)	6 (2)	0
Keratoacanthoma	1 (<1)	1 (<1)	18 (8)	0	0	0	2 (1)	0
Chorioretinopathy	1 (<1)	0	0	0	17 (7)	12 (5)	1 (<1)	0
Retinal detachment	0	0	0	0	9 (4)	6 (2)	5 (2)	1 (<1)
Decreased ejection fraction	0	4 (2)	3 (1)	0	2 (1)	14 (6)	3 (1)	0
QT-interval prolongation	8 (3)	2 (1)	3 (1)	0	6 (2)	2 (1)	1 (<1)	0

*The safety population was analysed according to the study treatment received. Eight patients assigned to the control group received investigational cobimetinib as a result of dispensing errors. Two patients (one in each study group) did not receive the assigned study drug and were therefore excluded from the safety analysis. Multiple occurrences of a specific adverse event for a patient were counted once at the highest grade of the occurrence, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. For example, if a patient had two episodes of a specific toxic event, one grade 3 and one grade 4, the patient was counted only once, in the grade 4 column. Similarly, in the “Any adverse events” row, if a patient had, for example, three separate events of grade 1, 3, and 4, the patient was counted only once, in the grade 4 column.
† The most common adverse events were those that occurred in at least 20% of the patients in either study group.

AEs that were more common with vemurafenib + cobimetinib than with vemurafenib + placebo included diarrhoea, photosensitivity, nausea and vomiting, elevated creatine phosphokinase (CPK) level, serous retinopathy and liver laboratory value abnormalities (predominantly elevated alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level). AEs that were less common with vemurafenib + cobimetinib than with vemurafenib + placebo included arthralgia, alopecia, and cutaneous neoplasms (specifically secondary cutaneous squamous cell carcinoma [cuSCC] and keratoacanthoma (Dreno 2014).

The frequency of grade 3 events was similar between arms (49% for each). Grade 4 AEs were more common with vemurafenib + cobimetinib than with vemurafenib + placebo (13% vs 9%), which was largely attributable to asymptomatic grade 4 CPK level elevation in 10 patients (4%) in the vemurafenib + cobimetinib arm compared with zero patients in the vemurafenib + placebo arm. The majority of first grade ≥3 AEs occurred early in treatment, with a median time to onset among patients with grade ≥3 AEs of 0.53 months for vemurafenib + cobimetinib and 0.79 months for vemurafenib + placebo. After the first cycle (28 days), the incidence of grade ≥3 AEs decreased over time. The median time to resolution for grade ≥3 AEs that occurred in the first 28 days was 0.5 months for both arms.

Extent of exposure to study treatment

Among the 254 patients in the vemurafenib + cobimetinib arm, the median number of cobimetinib cycles received was 7 (range 1 − 16 cycles), the median duration of cobimetinib exposure was 179 days (range 4 − 430 days), and the median dose intensity of cobimetinib was 97% (range 25% − 138%) (CSR).

The use of vemurafenib in the vemurafenib + cobimetinib arm was also assessed. Within the intervention arm, the median number of vemurafenib cycles received was 7 (range 1 − 16 cycles), the median duration of vemurafenib exposure was 183 days (range 9 − 430 days), and the median dose intensity of vemurafenib was 95% (range 23% − 107%).

Table 24 - AEs leading to discontinuation or dose modification (Dreno 2014)

AE, n (%)	Incidence (all grades)	Discontinuation	Reduction[a]	Interruption

	Vem + pbo	Vem + cobi	Vem + pbo	Vem + cobi	Vem + pbo	Vem + cobi	Vem + pbo	Vem +cobi
Diarrhoea	67 (28)	144 (57)	1 (<1)	0	0	6 (2)	6 (3)	14 (6)
Photosensitivity	75 (31)	105 (41)	0	0	0	0	1 (<1)	3 (1)
Rash	157 (66)	182 (72)	2 (1)	8 (3)	9 (4)	10 (4)	17 (7)	13 (5)
Elevated CPK	8 (3)	76 (30)	0	1 (<1)	2 (1)	0	0	4 (2)
Liver laboratory value abnormalities	76 (32)	101 (40)	3 (1)	8 (3)	3 (1)	4 (2)	5 (2)	9 (4)
Serous retinopathy	5 (2)	61 (24)	0	3 (1)	0	2 (1)	0	9 (4)
Cutaneous neoplasm	42 (18)	10 (4)	0	0	0	0	3 (1)	0

[a]Interruption or reduction of both drugs for AEs occurred in 33% of patients in the vem + pbo arm and in 42% of patients in the vem + cobi arm
vem + pbo = vemurafenib + placebo; vem + cobi = vemurafenib + cobimetinib

Serious adverse events

Serious adverse events (SAEs) occurred in 29.5% of patients treated with vemurafenib + cobimetinib and 25.1% of patients treated with vemurafenib + placebo (Table 25). The three most common SAEs in patients treated with vemurafenib + cobimetinib were pyrexia (2.4% of patients), dehydration (2.0%), and rash (1.6%). The three most common SAEs in patients treated with vemurafenib + placebo were pyrexia, keratoacanthoma, and pleural effusion (1.3% each). (CSR)

Table 25 - SAEs occurring in ≥1% of patients in either arm (safety evaluable population) (CSR)

SAE, n (%) – MedDRA preferred term	Vemurafenib + placebo (n=239)	Vemurafenib + cobimetinib (n=254)
Any SAE	60 (25.1)	75 (29.5)
Pyrexia	3 (1.3)	6 (2.4)
Dehydration	0	5 (2.0)
Rash	1 (0.4)	4 (1.6)
Rash maculo-papular	2 (0.8)	3 (1.2)
Increased alanine aminotransferase	1 (0.4)	3 (1.2)
Increased aspartate aminotransferase	1 (0.4)	3 (1.2)
Atrial fibrillation	0	3 (1.2)
Chorioretinopathy	0	3 (1.2)
Diarrhoea	0	3 (1.2)
Hypersensitivity	0	3 (1.2)
Keratoacanthoma	3 (1.3)	0
Pleural effusion	3 (1.3)	0
Retinal detachment	0	3 (1.2)

Grade 5 AEs

Overall, six deaths were attributed to adverse events in the vemurafenib + cobimetinib group and three deaths in the vemurafenib + placebo group (CSR). Of the six patients in the vemurafenib + cobimetinib arm, the AE was recorded as the primary cause of death for two patients (cardiac arrest and pneumonia). An additional two patients had primary cause of death recorded as “other” (unexplained; asthenia and fatigue). The remaining two patients with Grade 5 events had disease progression recorded as the primary cause of death.

Of the three patients with AEs graded 5 in the vemurafenib + placebo arm, cardiac failure was the reported cause of death for one patient and disease progression was documented as the cause of death for the other two patients.

Two patients, one in each treatment arm, died as a result of AEs that were considered by the investigator to be related to study treatment: One patient in the vemurafenib + cobimetinib arm (fatigue and asthenia) and one patient in the vemurafenib + placebo arm (cardiac failure).

4.12.3 Additional studies reporting safety

No additional studies were considered in relation to adverse reactions.

4.12.4 Provide a brief overview of the safety of the technology in relation to the decision problem.

The safety profile of cobimetinib in combination with vemurafenib has been evaluated in the coBRIM trial based on data from 254 patients with advanced *BRAF*-mutated melanoma receiving cobimetinib (median 7 cycles) at the proposed dose of 60 mg once daily in combination with vemurafenib 960 mg twice daily, at the clinical cutoffs of 9 May 2014 and 19 Sept 2014. An additional safety analysis will be conducted after the final OS analysis, expected [redacted].

Some of the key findings across the study were:

- The majority of common adverse events seen with the combination of vemurafenib + cobimetinib were of grade 1 or 2

- Permanent discontinuation of the combination due to AEs was relatively uncommon and rates of discontinuation were similar (12% in the control group and 13% in the combination group), indicating tolerability of the combination regimen

In the coBRIM study, several MEK inhibitor–specific toxic events were observed. An asymptomatic elevated creatine kinase level is a known class effect of MEK inhibition. 30% of patients in coBRIM with exposure to vemurafenib + cobimetinib experienced elevated creatine kinase; the majority of events (66%) being grade 1 or 2 and rapidly reversible. However, elevated creatine kinase was the most common grade 4 event (4%) seen with vemurafenib +cobimetinib therapy (Larkin 2014). In coBRIM, elevated creatine kinase was managed conservatively, usually with interruption or reduction of cobimetinib, and drug discontinuation was rare. 63% of grade ≥3 AEs resolved within 1 month of onset. Each study arm had 1 case of rhabdomyolysis; both resolved, and the patients continued study treatment (Dreno 2014).

MEK inhibitors are also associated with ocular conditions resembling central serous retinopathy in which fluid accumulates within the layers of the retina. In the coBRIM study, with surveillance ophthalmic examination, SR was observed in 63 patients (26%) in the vemurafenib + cobimetinib arm and 7 patients (3%) in the vemurafenib + placebo arm (de le Cruz-Merino 2015). Median time to initial onset of serous retinopathy events in the vemurafenib + cobimetinib arm was 1 month (range 0.1-9.3 months). The majority of cases (89%) of retinopathy in the coBRIM study were grade 1 (clinically asymptomatic) or 2 (moderate decrease in visual acuity) and were found to be reversible at subsequent ophthalmic examinations in the majority of cases without any treatment. For those requiring intervention, SR was managed with treatment interruption, dose reduction or with treatment discontinuation (de la Cruz-Merino 2015).

The SmPC recommends that all patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances are identified, an ophthalmologic examination is recommended.

Diarrhoea of any grade was twice as common with vemurafenib + cobimetinib as vemurafenib + placebo (57% vs 28%, respectively) and occurred earlier in treatment (Dreno 2014). In most cases, diarrhoea was effectively managed with antidiarrheal agents; no patients in the vemurafenib + cobimetinib arm discontinued either study drug, and relatively few required dose modifications (8% in the vemurafenib + cobimetinib group compared to 3% in the vemurafenib + placebo group). 75% of grade 3 diarrhoea resolved within 1 month of onset.

Photosensitivity, a known AE associated with BRAF-inhibitor therapy was more common with vemurafenib + cobimetinib than with vemurafenib + placebo, and grade ≥3 photosensitivity was reported in 3% and 0% of patients, respectively (Dreno 2014). Photosensitivity occurred throughout treatment in both arms. This AE was managed conservatively; no patients in either arm required discontinuation of either drug. Few patients required treatment interruption, 1% of vemurafenib + cobimetinib treated patients compared to <1% of vemurafenib + placebo treated patients.

Liver laboratory value abnormalities (predominantly elevated AST and ALT levels) of all grades were more common with vemurafenib + cobimetinib than with vemurafenib + placebo (40% versus 32%, respectively) as were grade ≥3 events, which occurred in 21% and 15% in the two arms, respectively (Dreno 2014). Most first events occurred early in treatment (median time to onset, 1.4 months for vemurafenib + cobimetinib; 0.95 months for vemurafenib + placebo). Management commonly involved dose modification (6% of vemurafenib + cobimetinib treated patients versus 3% of vemurafenib + placebo treated patients); vemurafenib was more often the drug modified in both arms. Most grade ≥3 liver laboratory value abnormalities resolved within 3 months of onset, 64% in the vemurafenib + cobimetinib arm and 67% in the vemurafenib + placebo arm.

Some toxic events were observed at a lower frequency in the combination group than in the control group, including keratoacanthomas (KA) and cutaneous squamous-cell carcinoma (cuSCC), alopecia, and arthralgias.

The most common cutaneous malignancies observed, cuSCC and KA, were reported less frequently in patients treated with cobimetinib plus vemurafenib (2.8%

for cuSCC and 0.8% for KA) than in patients treated with placebo plus vemurafenib (11.3 % for CuSCC and 8.4% for KA).

The decrease in frequency of cuSCC and KA observed in the vemurafenib + cobimetinib arm is not unexpected and has been observed in previous studies combining a BRAF and a MEK inhibitor (Ribas 2014). The development of these lesions is driven by *RAS* and consequently MAPK signalling in patients receiving BRAF inhibitors. Part of the rationale for investigating the combination of a BRAF and a MEK inhibitor was to block the paradoxical activation of the MAPK pathway induced by single-agent BRAF inhibitors, and thus decrease the frequency of cuSCC and KA (Su 2012).

In summary, these data indicate that the combination of cobimetinib with vemurafenib is well tolerated. The combination of a MEK inhibitor with vemurafenib results in different types and frequencies of AEs. However, most of these events were Grade 1 or 2, occurred early in the treatment course, and were fully or partially reversible. Discontinuation of study drugs due to toxicity was uncommon and rates of discontinuation due to AEs were generally comparable between the treatment arms. The increased efficacy of the combination of cobimetinib with vemurafenib, does not appear to add unexpected or unmanageable toxicities. Consequently cobimetinib in combination with vemurafenib is not expected to add any significant burden to patients, their healthcare professionals or cost to the NHS.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 A statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology.

Clinical evidence for cobimetinib + vemurafenib is taken from a large, double-blind, randomised, placebo controlled phase III clinical trial, the coBRIM study. The patients enrolled in this study are consistent with the cobimetinib Marketing Authorisation, and the population specified in the decision problem. The study recruited a total of 495 patients, with 11 UK centres taking part, recruiting 29 patients between them.

It is reasonable to assume that the responses seen of patients in the coBRIM study are the responses which can be expected with cobimetinib + vemurafenib in clinical practice. At the time of recruitment into the study, there were multiple treatment options available for patients with BRAF V600 mutation-positive melanoma, including stargeted therapy and immunotherapy. Patients were recruited into the study once a clinical decision had been made to treat with targeted therapy. This same decision point will be made in clinical practice in the UK. As such the responses seen in the coBRIM study can be expected by UK patients.

The coBRIM study met its primary endpoint of a statistically significant improvement in PFS, as compared to vemurafenib monotherapy, assessed at the primary data cutoff in May 2014. An additional PFS analysis was conducted in January 2015 at the request of the EU assessors, and the final OS analysis was conducted in August 2015.

The most recent analysis of the coBRIM study (August 2015) has shown a statistically significant (p= 0.005 HR 0.70 (0.55-0.90)) improvement in median OS of almost 5 months between treatment arms, 22,3 months (95% CI, 20.3-NE) for vemurafenib + cobimetinib compared to 17.4 months (95% CI, 15.0-19.8) for vemurafenib and placebo. At the January 2015 data cutoff, median PFS for vemurafenib + cobimetinib was 12.3 months (95% CI, 9.46 - 13.37) compared with 7.2 months (95% CI, 5.55 - 7.49) in patients treated with vemurafenib and placebo; HR 0.58 (95% CI, 0.46 - 0.719) (see Figure 6 and Table 16; Larkin, 2015).

Vemurafenib + cobimetinib, was associated with improved symptoms, functional impact, and health-related quality of life, compared to patients receiving vemurafenib + placebo, as measured by the EORTC QLQ-C30. Overall, a higher percentage of patients in the combination arm had clinically meaningful improvement in symptom scores from baseline for all EORTC domains (functioning and symptoms). Cobimetinib and vemurafenib provides superior efficacy and symptom improvement for pain (7%), fatigue (9%), social functioning (11%), and insomnia (16%) compared with vemurafenib alone (Dreno, 2015).

The benefit in OS and PFS with vemurafenib + cobimetinib therapy is evident in all the pre-specified patient subgroups (Larkin, 2014)

The combination of cobimetinib with vemurafenib is well tolerated, with the majority of AEs reported during the study being of Grade 1 or 2 severity. Most AEs occurred early in the treatment course, and were fully or partially reversible. Discontinuation of study drugs due to toxicity was uncommon and rates of discontinuation due to AEs were generally comparable between the treatment arms. The increased efficacy of the combination of cobimetinib with vemurafenib, does not appear to add unexpected or unmanageable toxicities.

4.13.2 Strengths of the clinical evidence base .

Cobimetinib + vemurafenib has been approved for use by the EMA and FDA, Approval was based on the coBRIM study (along with relevant pre-clinical studies). The coBRIM study was rigorously designed and conducted, and compared cobimetinib + vemurafenib to the standard of care at that time, vemurafenib monotherapy (a comparator in the decision problem). The patient population recruited into the study is consistent with the granted Marketing Authorisation, and the population of the decision problem.

The primary aims of treatment in metastatic melanoma are to reduce tumour burden, delay disease progression and prolong life. The primary and secondary endpoints of the coBRIM study; PFS and OS respectively; allowed assessment of the efficacy of cobimetinib + vemurafenib in achieving these clinical aims.

4.13.2 Limitations of the clinical evidence base

Whilst not a limitation of the coBRIM study design, there is a lack of clinical evidence for comparison of cobimetinib + vemurafenib to dabrafenib (the second comparator of the decision problem).

Due to the recent approval of cobimetinib + vemurafenib there is limited real-world clinical experience. However, as described above, the responses seen in the coBRIM study can be expected by non-trial, UK patients.

4.13.2 Relevance to clinical practice

For the majority of patients in the UK with BRAF V600 mutation positive metastatic melanoma, treatment with a BRAF inhibitior is the standard of care. The coBRIM

study demonstrated a statistically significant improvement in PFS and OS for these patients when treated with cobimetinib + vemurafenib, as compared to vemurafenib monotherapy. The efficacy provided by combination therapy with a BRAF and MEK inhibitor means it is anticipated combination therapy will replace use of BRAF inhibition alone.

The coBRIM study included 29 UK patients, from 11 UK centres. This therapy area is highly dynamic, with new treatment options available and anticipated in the future. At the time of recruitment into the coBRIM study, there were various other treatment options available, including alternative clinical studies. As recruitment into coBRIM meant a clinical decision had been made to treat with targeted combination therapy, it is anticipated this same clinical decision will trigger treatment with cobimetinib + vemurafenib in UK clinical practice. Therefore the responses seen in the study are anticipated to translate into UK clinical practice, and are considered highly relevant.

4.13.2 End-of-life Assessment

We believe the treatment of cobimetinib + vemurafenib in unresectable or metastatic melanoma patients meets end of life criteria.

Table 26 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Patients with advanced melanoma have a 1-year survival rate of 25% and a median overall survival of approximately 6 months (Jarkowski, Norris and Trinh, 2014).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The median OS data presented at SMR in November 2015 by Atkinson et al, provides evidence that treatment with vemurafenib and cobimetinib provides more than an additional 3 months. The median OS data show a statistically significant increase of nearly 5 months.
The treatment is licensed or otherwise indicated for small patient populations	It is estimated that approximately 576 patients per annum will be eligible to receive vemurafenib and cobimetinib for BRAF mutation-positive unresectable or metastatic melanoma, in England and Wales. We have assumed that 10,650 patients in England and Wales will develop malignant melanoma. Of these 22% will have advanced melanoma in England and Wales (2343 patients). Of 34% will have mutated BRAF V600 gene. Of the patients that are BRAF mutated the majority will be treated with BRAF inhibitors. An assumed 12% will enter clinical trials. (Roche 2016) As such there are 576 patients who are eligible for vemurafenib and cobimetinib treatment in England and Wales.

4.14 Ongoing studies

4.14.1 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 final OS and PFS results from coBRIM have now been presented, with publication in a peer reviewed journal anticipated [redacted]. There are no additional ongoing studies. Updated safety analysis from the August 2015 coBRIM data cut is ongoing, with results anticipated [redacted].

5. Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1-5.1.3 Search strategy for cost-effectiveness studies

A SLRwas performed to identify cost-effectiveness evidence for cobimetinib in combination with vemurafenib for the treatment of metastatic or unresectable BRAF V600 mutation-positive melanoma. The searches were performed on 9 and 10 December 2015. A date limit from January 2000 to December 2015 was applied. Details of the search strategy and the results for the SLR are provided in appendix 9.

The SLR did not identify any economic evaluations relevant to the current HTA submission

5.2 De novo analysis

Patient population

5.2.1 Patient groups included in the economic evaluation

The de novo analysis will assess use of cobimetinib + vemurafenib as a first line treatment option for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. This population is consistent with both the appraisal scope and Marketing Authorisation.

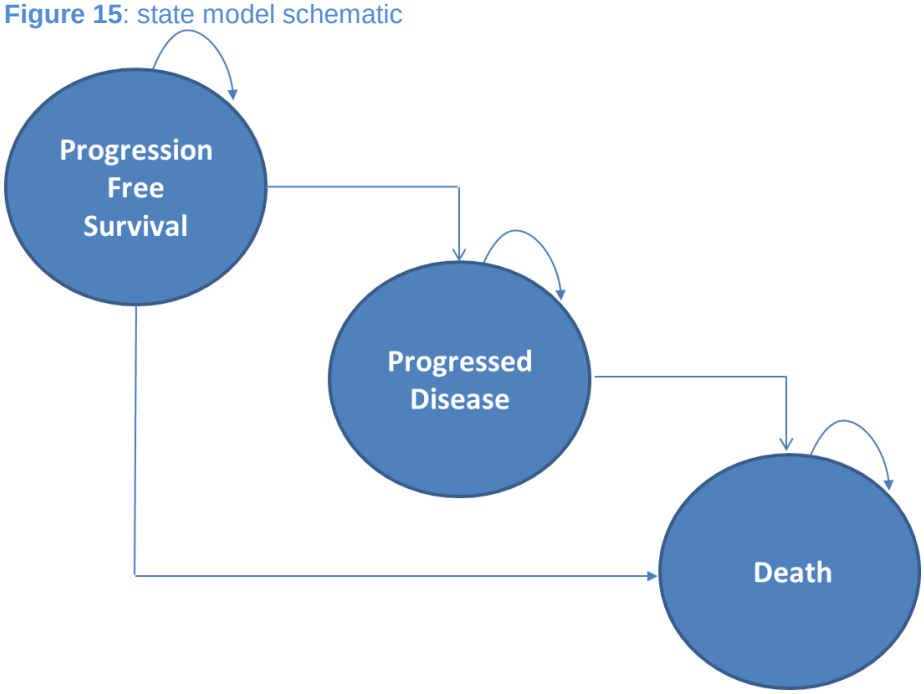
As stated in the appraisal scope, current UK clinical practice for patients with BRAF mutation-positive advanced melanoma is first-line treatment with a BRAF inhibitor. The coBRIM (Larkin, 2014) study evaluated the efficacy and safety of cobimetinib + vemurafenib, vs. vemurafenib alone, in a patient group consistent with the scope. The patient population considered in this analysis, therefore, also match the scope.

Model structure

5.2.2 Model structure

A partitioned survival model with 3-states: ‘progression-free-survival’, ‘progressed disease’ (PD) and ‘death’ (see Figure 15 below) has been developed.

Figure 15: state model schematic



This model was considered appropriate for the decision problem. The structure and health states are closely aligned with the clinical pathway (NICE Melanoma Pathway) identified in section 3, and are consistent with the approaches used in earlier NICE appraisals of treatments for metastatic melanoma (TA269 2012; TA319 2014; TA321 2014; TA366 2015).

The primary aims of treatment in metastatic melanoma are to reduce tumour burden, delay disease progression and prolong life.

The PFS health state captures patients who are responding to treatment either through reduced tumour burden, or stabilised disease. In this state patients have a higher quality of life, compared to PD.

Use of the PD state is consistent with the anticipated Marketing Authorisation, which states: 'Treatment with Cotellic should continue until the patient no longer derives benefit'. The model derives the proportion of patients in the PD health state as the difference between the PFS and overall survival curves. This is therefore capturing the disease state for which treatment with cobimetinib would cease.

The model does not assume any subsequent lines of anti-cancer therapy, following progression on the intervention or a comparator. Whilst clinical advice provided to

Roche suggests that patients would go on to receive subsequent therapies, there is a lack of data to allow robust incorporation of such a treatment pathway into the model. Although coBRIM captured the proporation of patients receving a treatment at 2nd, 3rd of 4th line, the type of treatment recived was only reported across all lines – i.e. the sequence is not available (Table 27). Furthermore, data on dose received, treatment duration, and clinical outcomes were not reported. Similarly limited data are available on the post-progression treatments received for patients receiving dabrafenib in the COMBI-d or BREAK-3 studies (Long 2015; Hauschild 2012).

Table 27: Summary of post end of study anti-cancer treatment (coBRIM safety population)

	Cobimetinib + vemurafenib	**Vemurafenib**
Treatments received across all lines		
Chemo / non-anthra cycline therapy	4.3%	5.4%
Biologic therapy	3.9%	2.9%
Immunotherapy	4.7%	7.1%
Other	3.6%	4.2%
Line of therapy		
2nd line	14.2%	15.9%
3rd line	2.0%	2.9%
4th line	0.4%	0.0%

The information available from coBRIM does, however, suggest that the frequency and type of subsequent anti-cancer therapy administered did not differ by trial arm (Table 27). This implies the impact of including these therapies would not have a significant differential impact on treatment costs by comparator arm.

Therefore, as a number of assumptions would be required to implement the use of post-progression treatments in the model, and there are data which suggest the impact of doing so would be limited, these treatments were not included in the

model. This approach is also consistent with prior melanoma appraisals for first-line therapies (TA269 2012; TA319 2014; TA321 2014; TA366 2015) .

The cycle length of the model is one week, with the proportion of patients in each health state calculated every 7 days. A half cycle correction has been applied in the model.

5.2.3 Features of the de novo analysis.

Table 28 Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	30 years	Sufficient to capture all meaningful differences in technologies compared and consistent with previous metastatic melanoma appraisals
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case
Discount of 3.5% for utilities and costs	Yes	NICE reference case
Perspective (NHS/PSS)	Yes	NICE reference case
PSS, personal social services; QALYs, quality-adjusted life years		

Intervention technology and comparators

5.2.4 Implementation of intervention and comparators in the model

The intervention (cobimetinib in combination with vemurafenib) and comparators (vemurafenib monotherapy or dabrafenib monotherapy), are assessed in line with their existing licensed indications. This is also consistent with the decision problem (see section 1.1).

5.2.5 Treatment continuation rules

According to both the intervention and comparator indications, patients receive treatment until disease progression or unacceptable toxicity. This is consistent with clinical practice and the coBRIM study design. It is reasonable to assume this assessment of disease progression, and therefore trigger for treatment

discontinuation, will not require additional resource use, or changes to current routine clinical practice.

Section 5.5.2 includes further details of time on treatment assumptions.

5.3 Clinical parameters and variables

5.3.1 Describe how the clinical data were incorporated into the model

Clinical trial results for cobimetinib + vemurafenib are available from the coBRIM study. As outlined in section 4.2.1 this is considered the most appropriate source of clinical evidence for the intervention, and directly compares to vemurafenib monotherapy, a key comparator for this appraisal. As such this study is the main data source for the intervention and one comparator; providing clinical outcomes, adverse events, treatment dose and duration of treatment. An indirect treatment comparison was conducted (see section 4.10) to allow comparison of the intervention to dabrafenib monotherapy.

The model structure includes three health states, PFS, PD and death. PFS and OS outcomes are available directly from the coBRIM study, as the primary and secondary endpoints respectively. These outcomes are also consistent with the appraisal scope.

It is reasonable to assume the responses seen in patients participating in the coBRIM study are the responses which can be expected with cobimetinib + vemurafenib in UK clinical practice.

At the time of recruitment into the study, multiple treatment options were available for patients with BRAF V600 mutation-positive melanoma: broadly,targeted therapies and immunotherapies. Patients were recruited into the study once a clinical decision had been made to treat with targeted therapy. This same decision point will be made in clinical practice. We therefore incorporate clinical parameters using results from the coBRIM study, without any adjustment for responses in the trial being different than anticipated in clinical practice

5.3.2, 5.3.3 Extrapolation of clinical data in the model

PFS and OS results from coBRIM are extrapolated to the 30 year time-horizon (Table 28 for time-horizon justification). The proportion of patients in the PD health state at any time-point is calculated as the difference between the PFS and OS curves. As life-time results are not available for all patients in the coBRIM study, it is necessary to extrapolate the PFS and OS results to meet our 30 year time-horizon.

PFS Extrapolation

The established approach for extrapolation –fitting alternative distributions to the observed KM data from the trial through parameterisation –was undertaken.

The following candidate distributions were fitted to the observed PFS data from the coBRIM study: Log Logistic, Weibull, Log Normal, Gamma, Gompertz and Exponential. The goodness of fit for these functions was assessed using Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and visual assessment of each fitted curve against the observed data. Based on the AIC and BIC statistics (Table 29) and visual inspection, the LogLogistic distribution was considered to be the most appropriate functional form. The extrapolations applied to trial data in both arms are illustrated in Figure 16. Alternative extrapolations are explored in scenario analysis is section 5.8 and are presented in Appendix 10.

The joint estimation of LogLogistic survival curves for the two groups, including common shape parameters and a coefficient that captures the differences between the two groups, hinges on the LogLogistic assumption and the proportional odds assumption. The LogLogistic assumption requires that the relationship between time and the survival probability is accurately described by a logistic function. The proportional odds assumption requires that the odds of dying differ between the two treatment groups by a constant ratio, over the entire survival time. These assumptions can be validated using a plot of the log survival odds ln(S(t)/(1-S(t))) against the log of time ln(t). The lines of the log-odds curves are straight and parallel in both treatment groups which confirms that the parametric curves can be estimated using a log-logistic function with common shape parameters for both treatment groups (Figure 17).

Alternative parametric distributions are explored in the scenario analyses in section 5.8.8, and are presented in Appendix 10.

Table 29 Summary of parametric function goodness of fit for PFS

Distribution	Log Likelihood	AIC	BIC
EXPONENTIAL	-604.1028	1212.2056	1220.6147
WEIBULL	-587.1677	1180.3353	1192.949
LOG-LOGISTIC	**-575.6147**	**1157.2293**	**1169.843**
LOG-NORMAL	-577.0653	1160.1306	1172.7443
GAMMA	-576.1995	1160.399	1177.2172
GOMPERTZ	-598.9732	1203.9463	1216.56

Figure 16 Parametric (LogLogistic) and KM estimates for PFS

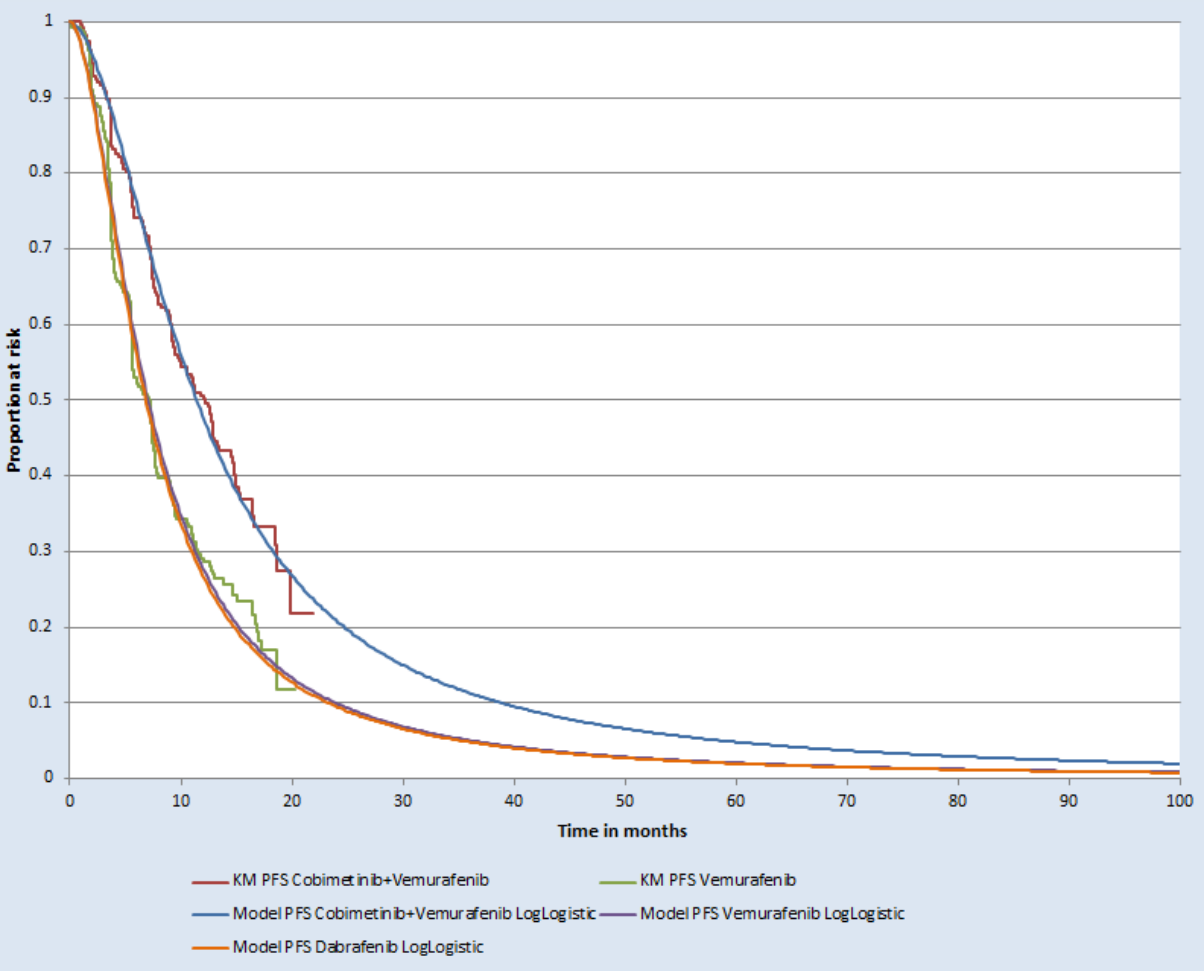
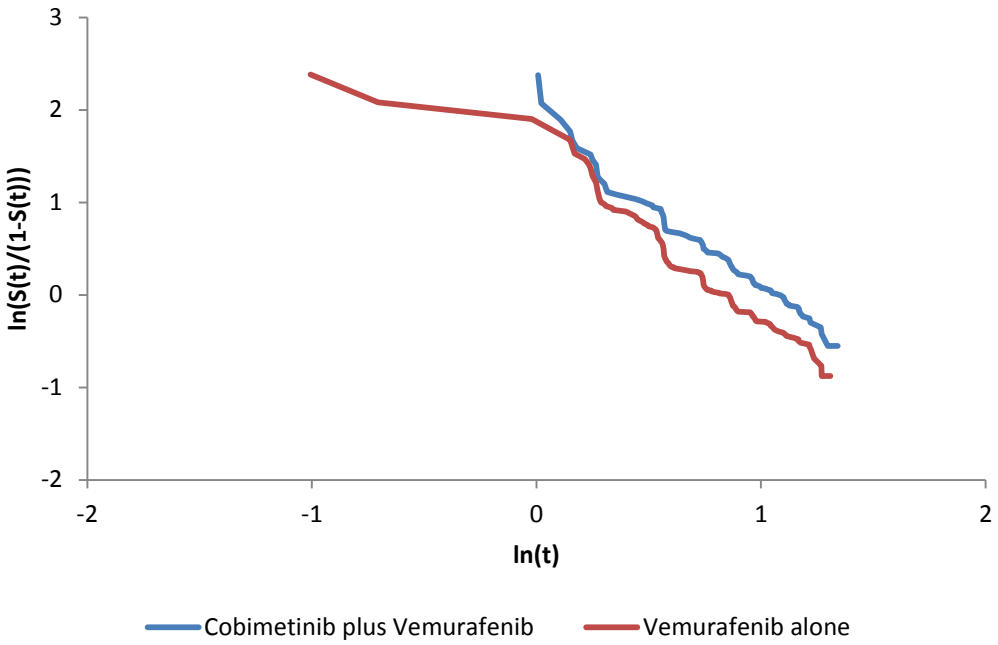


Figure 17 Diagnostic plot assessing the proportional odds odds assumption



Comparison of the modeled median PFS was comparable with the median PFS of observed patients in the coBRIM study, thus validating the model results (see Table 48).

OS extrapolation

Data from melanoma registries and long-term analysis of clinical trials for melanoma therapies suggest the risk of death for patients with metastatic melanoma declines over time, with risk being conditional upon the time since initial diagnosis (Xing, 2010). Figure 18 and Figure 19 demonstrates that the rate of death for stage IV metastatic melanoma patients considerably decreases after 5 years.

With relatively immature data from the coBRIM study, use of traditional parametric survival analysis which relies on this observed data for cobimetinib + vemurafenib, will fail to account for this change in mortality rate.

Figure 18: KM estimates of 5 year OS from phase III study comparing ipilimumab to dacarbazine in metastatic melanoma (Maio, 2015)

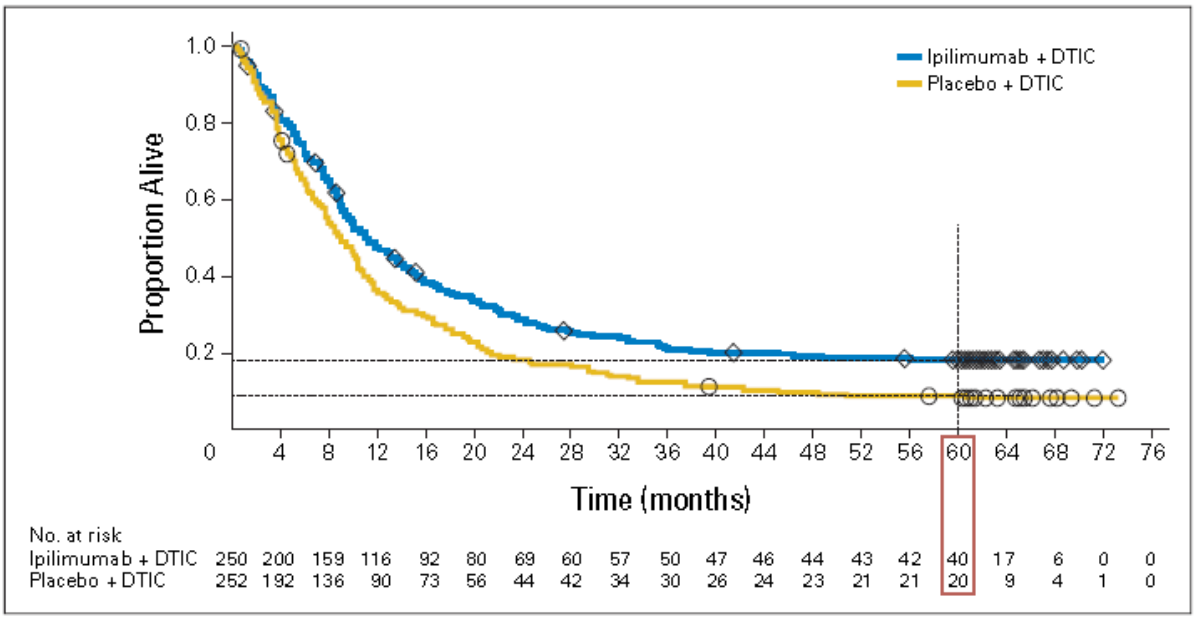
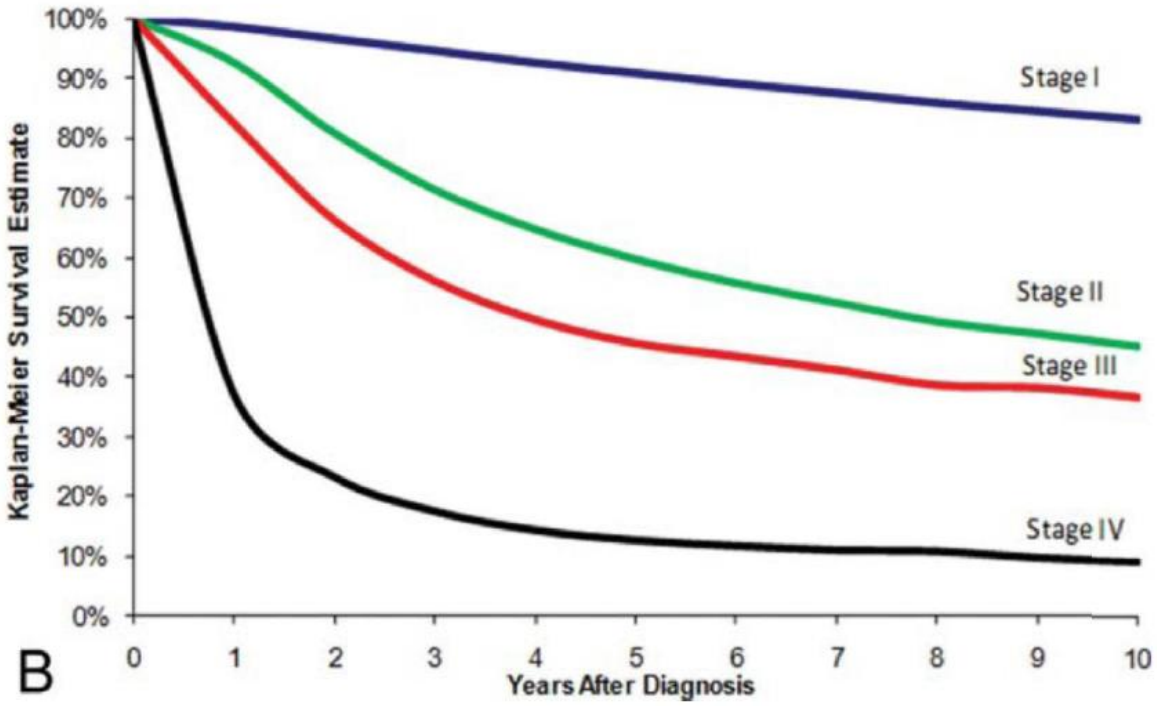


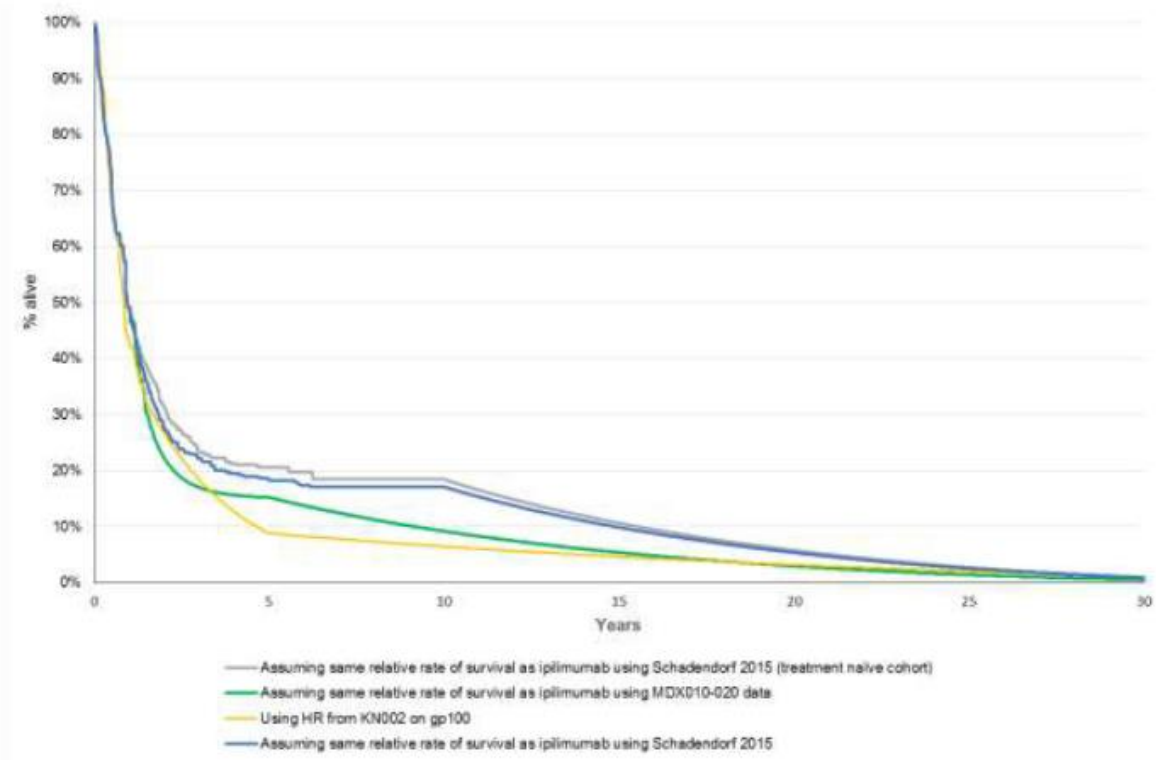
Figure 19: SEER registry melanoma OS curves by disease stage (Xing, 2010)



Prior melanoma NICE appraisals have utilised various methodologies to account for this change in mortality rate. Recent pembrolizumab appraisals (TA357 and TA366 2015) used a piece-wise exponential function fitted to pembrolizumab trial data (year

1), long-term ipilimumab data (years 2 -7) and registry data for years 7 onwards (Figure 20 below).

Figure 20: OS extrapolation from manufacturer submission for TA357 (figure 36, page 165)



Critique and feedback from the ERG during this appraisal proposed a mixed survival model would be more appropriate, as the piece-wise model resulted in clinically implausible outcomes. Use of the mixed survival model was also proposed during the vemurafenib monotherapy technology appraisal, TA269, 2012.

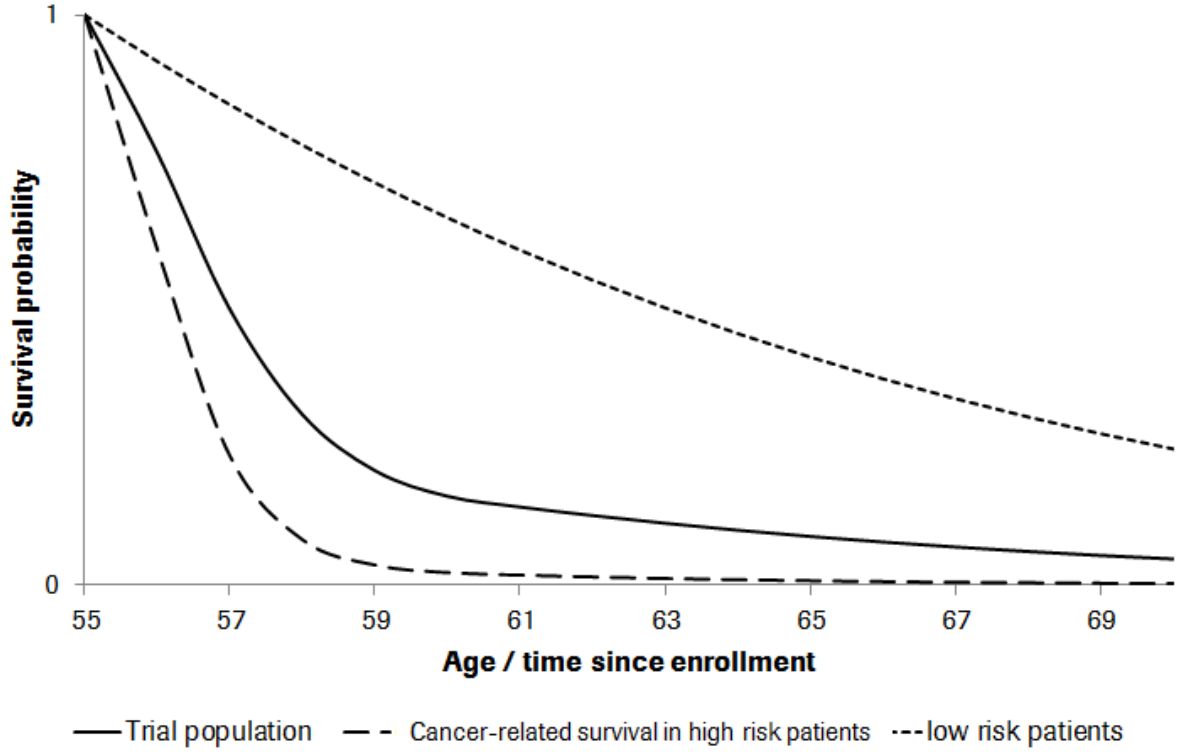
Taking into account review of prior appraisals, the OS estimates for this analysis were modeled using the mixture cure-rate methodology.

The mixture model accounts for the decrease in cancer-related mortality risk over time (as demonstrated in Figure 18 and Figure 19 above). Statistically, this decrease in the cancer-related mortality risk is accounted for by an estimation of the overall mortality risk at a given point in time, as a mixture between the cancer-related and background mortality risk. The estimation uses a dataset including the observed survival times in the coBRIM trial and the background mortality risks from life-tables. The weight assigned to the background mortality is referred to as the “cured fraction”. However this ‘cure rate fraction’, should not be interpreted as a clinical

'cure' from melanoma. Rather, the proportion of patients for whom their disease is stable, and the risk of death attributable to cancer is equivalent to the risk of death from other causes. This can be interpreted as a proportion of patients whom are as likely to die of non-cancer causes as from cancer.

These two populations (those with low risk of cancer related death, and those with high risk of cancer related death) are combined to produce an average survival for the whole population, illustrated in Figure 21 below.

Figure 21 Stylised illustration of cause-specific survival rates



The trial population survival is expressed as S(t), and incorporates the patients at high risk of cancer-related death [$S_c(t)$], and the patients at low risk [$S^b(t)$]. The 'cure fraction' is expressed as π

$$S(t) = S^b(t)\pi + (1-\pi)S^b(t)S_c(t)$$

Calculating the proportion of patients at low risk of cancer-related mortality:

To ascertain the ‘cure fraction’, the Surveillance, Epidemiology, and End Results (SEER) database was used.

Long-term mortality due to metastatic melanoma was extracted from the SEER registry. Within the registry, the specific disease of interest was selected according to the criteria specified in Table 30 below.

Table 30 Variables used to define a melanoma-specific population within the SEER registry

Variable	**Value**
Site recode ICD-O-3/WHO 2008	Melanoma of the Skin
Behavior recode for analysis	Malignant
AYA site recode/WHO2008	7.1 Melanoma

The year of diagnosis, age at diagnosis, gender, event time and censoring were extracted from the registry. As the SEER registry recruits US patients, US life tables were used to determine background mortality. Taking into account the patient characteristics listed above, the survival hazard and rates were obtained for each subject. Parametric functions were fit to determine the cure rate fraction. As seen in Table 31, the lognormal and generalized gamma exhibited the best fit according to the AIC and BIC criterion.

Table 31 [redacted].

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

The long-term data available from the SEER registry allows direct comparison of the parametric function to the KM. The [redacted] represented a better fit to the tail of the KM, as such was selected (Figure 22 below).

Figure 22 [redacted]

The resulting cure fraction is [redacted]. This is interpreted as [redacted] of patients whose risk of death due to cancer is equal to their risk of death due to non-cancer causes.

The 'cure fraction' calculated from the SEER database (π_{SEER}) is subsequently incorporated into the parametric model fit to the coBRIM study results. The cure rate fraction of the study is a constrained optimization problem, such that $\pi_{trial} = \pi_{SEER}$, thus assuming no effect of treatment on the proportion of patients with low, long-term risk of mortality due to cancer – the 'cure fraction'.

Generating parametric models for OS from coBRIM

Patients recruited in the coBRIM trial were both male and female, of various ages and countries of origin. These aspects are known to affect the background mortality of an individual. Therefore to accurately extrapolate the OS curve beyond the follow up of coBRIM, these patient level data (gender, nationality, and age) were included in the analysis.

The SEER population are older than coBRIM patients. As such the background survival for subjects in the coBRIM study is used in the base-case analysis, including all countries taking part in the study.

The Exponential, Weibull, LogLogistic, LogNormal, Gompertz, Gamma and Generalized Gamma, parametric models were fit to both the cobimetinib + vemurafenib and vemurafenib arms of the coBRIM study. The parametric models incorporated the 'cure fraction', coBRIM hazard and coBRIM specific background mortality.

Table 32 [redacted]

[redacted]

According to visual fit and the AIC and BIC criterion (Table 32 above), the [redacted] function was the most appropriate fit when considering both treatment arms. Figure 23 shows a comparison of coBRIM KM curves, parametric estimates and the SEER melanoma KM curve. Alternative parametric distributions are explored in the scenario analyses in section 5.8.8, and are presented in Appendix 10.

As discussed above, patients in the SEER registry are older, with an early date of diagnosis, thus yielding a lower background survival curve. This effect is seen in Figure 23, as the coBRIM curves do not meet the SEER curve; an expected outcome given the differences in the populations of the studies.

Figure 23 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Dabrafenib

For the ITC with the second comparator, dabrafenib, results of the NMA are incorporated in the model in terms of AFT values. The OS parametric models incorporated the 'cure fraction' and AFT values from the ITC. In the absence of patient level data on dabrafenib, the adjustment for background mortality rates (to use within the mixture model) has been based on the coBRIM patient population. Results of the OS extrapolation can be seen in Figure 24

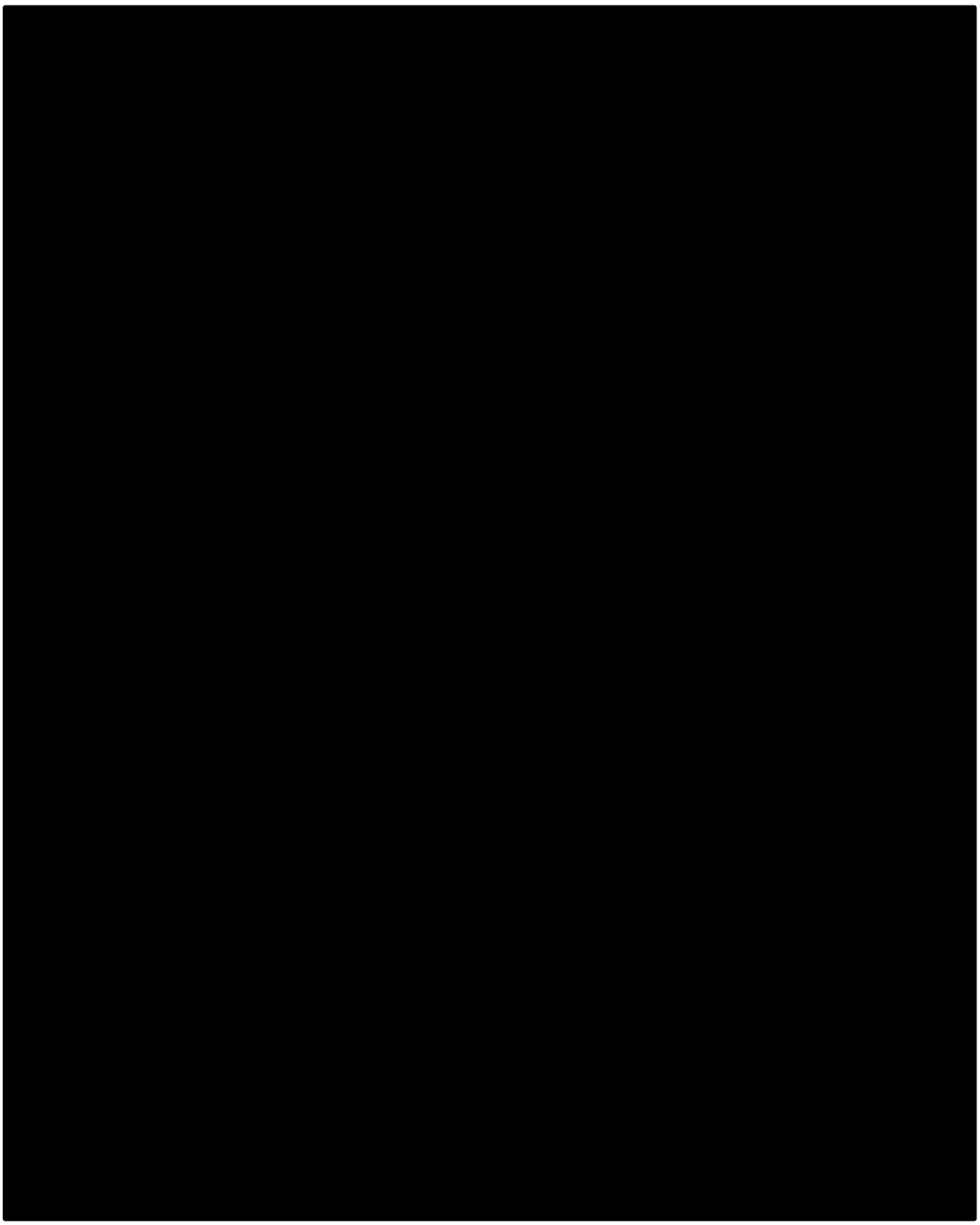
Figure 24 [redacted]

[redacted]

Summary

The resulting parametric curves for cobimetinib + vemurafenib, and vemurafenib monotherapy, fit to coBRIM data are shown in Figure 25. Scenario analyses in section 5.8.8 explore alternative parametric functions.

Figure 25 [redacted]



5.3.4 Clinical experts assessment of the applicability of the clinical parameters

An advisory board was conducted with two Medical Oncologists specialising in melanoma and three Health Economists. Experts were selected based on their area of expertise and experience in melanoma HTAs.

The experts confirmed the methodological and clinical plausibility of the mixture-cure model to extrapolate survival data from the coBRIM study, and suggested this was an improved approach as compared to methods in prior melanoma HTAs.

5.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

5.4.1 Health-related quality-of-life (HRQL) data collected in the clinical trial

HRQoL data were collected as a secondary endpoint during the coBRIM (Larkin, 2014) study. Patient-reported outcomes included EORTC QLQ-C30 and EQ-5D-5L. Both questionnaires were translated into patient local language as appropriate.

EORTC QLQ-C30 and EQ-5D-5L were administered to patients enrolled in the coBRIM study, in both treatment arms. Patients completed both questionnaires on study visit days prior to starting any other study-related assessments, and for Cycle 1 Day 1, prior to initiating study treatment.

For patients receiving cobimetinib + vemurafenib a total of 1323 observations were obtained, and 1103 for patients receiving vemurafenib. These results allowed generation of utility values for patients in PFS. Limited observations (n=57) are available for patients in the PD state.

Use of EQ-5D-5L results for expression of health effects is appropriate for this CEA, and is consistent with the reference case. Elicitation of HRQoL was directly from patients having received the technology or comparator (vemurafenib monotherapy), and using the preferred measure of HRQoL, the EQ-5D. Details of the algorithm to express EQ-5D-5L as utilities can be found in section 5.4.2 below.

Mapping

5.4.2 Mapping methods used to estimate health state utility values from the quality-of-life data collected in clinical trials.

Preference values for EQ-5D-3L have been elicited from a large UK population using the time trade-off method (Dolan, 1995) , and are well established for deriving index-based values for the EQ-5D scores. The coefficients used to generate UK utility

values from the EQ-5D-3L (Dolan, 1995) are not directly applicable to the new instrument.

Two methods have been proposed to calculate utility scores for the EQ-5D-5L in UK patients. The first uses a "crosswalk" between the 3L and 5L versions (van Hout B, 2012). A calculator for this conversion is available on the EuroQoL website (EQ-5D-5L Value Sets, 2015).

The second method is based on a new scoring algorithm for the general population presented by the Office of Health Economics (Office of Health Economics, 2014). Preference-based valuation of EQ-5D-5L sets was conducted by OHE using a protocol developed by the EuroQol Group. The interviews were conducted in England. Both the crosswalk, and OHE algorithm have been validated (EuroQol website 2016) as appropriate methods for calculation of utility scores using the EQ-5D-5L.

Utilities generated for the PFS health state from the coBRIM EQ-5D-5L results, using both the crosswalk and OHE scoring algorithm were discussed with expert advisors (see section 5.4.13 below). Whilst the OHE algorithm is preferred as it is specific to England and avoids the requirement to 'crosswalk' or 'map' the values, this method resulted in high utilities (Table 33). In fact these values were higher than general population norms for the average age of patients in the coBRIM study. Advisors deemed these results clinically implausible, and suggested the crosswalk values were more appropriate.

Table 33 Utility values using 2 methods to convert EQ-5D-5L values from coBRIM

	Treatment	Crosswalk	OHE algorithm
PFS	Cobimetinib + vemurafenib	0.837	0.898
	Vemurafenib	0.817	0.887
PD	Cobimetinib + vemurafenib	0.798	0.862
	Vemurafenib	0.801	0.865

Health-related quality-of-life studies

5.4.3 Systematic searches for relevant HRQL data.

A SLR was conducted on 10 March 2015, and updated on 9 December 2015, to identify health state utility values (HSUVs) for patients with advanced (unresectable or metastatic) melanoma. The SLR was initially kept broad to identify utility values derived using any instrument, or mapping algorithms that would allow disease-specific or QoL scores to be translated to utilities. Studies considered most appropriate to inform the economic model, were those which reported utility data for relevant health states, derived using methods consistent with the NICE reference case. Table 34 details the inclusion and exclusion criteria applied in the search. Full search strategy and results are provided in appendix 11.

Table 34 HSUV studies systematic search: inclusion and exclusion criteria

	Inclusion criteria	**Exclusion criteria**
Population	Advanced (unresectable or metastatic) melanoma	Early stage melanoma
Interventions	Not restricted by intervention	
Outcomes	Utility values elicited using the following techniques: • Time trade-off (TTO) • Standard gamble (SG) • Generic preference based instruments Mapping studies that would allow disease specific measures (e.g. EORTC QLQ-C30, FACT-M) to be mapped onto preference based utilities	Measures of quality of life (QoL) other than utility /disutility values Visual analogue scale scores (VAS)
Study design	Not restricted by study design	
Country	Not restricted by country	
Date restrictions	Original SR: No restriction applied Update SR: 2015 to December 2015	
Language restrictions	English language	Non-English languages
Publication type	Primary paper, congress abstracts	Review, editorial, letter

5.4.4 Details of the studies in which HRQL was measured.

The SLR did not identify any studies which were considered appropriate to the appraisal scope. Full tabulated details are provided in appendix 12 including rationale for study exclusion.

In total, 17 publications (including one mapping algorithm (Askew et al., 2011) met the inclusion criteria of the combined original and update SLRs. Of these, two reported HSUVs consistent with the NICE reference case (Paly et al., 2015, Hatswell et al., 2014), seven reported HSUVs that were not consistent (Harrison and Kim, 2015, Tromme et al., 2014)(Curl et al., 2014)(Askew et al., 2011) (Coleman King et al., 2011) (Hogg et al., 2010, Beusterien et al., 2009), and in a further eight studies, it was unclear if HSUVs were in line with the reference case requirements.(Batty et al., 2011 , Batty et al., 2012, Beusterien et al., 2003, Ko et al., 2003, Long et al., 2015, Grob et al., 2015, Abernethy et al., 2015, Porter et al., 2014). Six of the 17 reported utilities derived using the EQ-5D. However, none were considered appropriate to inform the economic model, as the HSUVs were specific to treatment with nivolumab and dacarbazine (Harrison and Kim, 2015, Paly et al., 2015) (Long et al., 2015), dacarbazine plus trametinib or vemurafenib (Grob et al., 2015), or ipilimumab and nivolumab (Abernethy et al., 2015) (one study did not report treatment detail for patients (Tromme et al., 2014)). In addition, utility data from five of the six publications reporting EQ-5D utilities were not consistent with the NICE reference case (or there was limited information reported to assess consistency with the reference case).

The SLR identified one mapping algorithm for converting Functional Assessment of Cancer Therapy-Melanoma (FACT-M) scores to EQ-5D 3L utilities, however, this was not considered relevant to the economic model.

The SLR identified one study which has been used in a prior NICE technology appraisal in melanoma, TA269 2012. The study by Beusterien et al. (2009) was conducted in the UK and Australia to elicit utilities for advanced melanoma health states among members of the general public. The health states valued include: ‘partial response’; ‘stable disease’; ‘progressive disease’; and ‘best supportive care’; as well as utility decrements for toxicities. UK specific results are reported in the study. This study is not consistent with the reference case as utilities were not

elicited directly from patients. However in the absence of available utilities for patients in progressed disease, and progressed stable disease, these data provide UK specific results.

5.4.5 Key differences between values derived from the literature search and those reported in or mapped from the clinical trials.

As described above, no utility values derived from the literature were deemed appropriate to this cost-effectiveness study.

To date there are four published, and one ongoing NICE technology appraisals for first-line treatments in metastatic melanoma (TA269 2012, TA319 2014, TA321 2014, TA366 2015; ID845 2016). Comparison of the EQ-5D-5L utility values from the coBRIM study (via crosswalk), and these prior first-line appraisals are summarised in Table 35 below:

Table 35 Comparison of utility values from prior NICE technology appraisals relevant to scope population

Health state	Vemurafenib	Dabrafenib	ipilimumab	pembrolizumab	nivolumab	Cobimetinib +vemurafenib
PFS	0.85	0.77	-	-	-	0.832
PD	0.59	0.68	-	-	-	0.798
PFS≥ 30 days					0.8018	
PFS< 30 days					0.7795	
PD≥ 30 days					0.7277	
PD< 30 days					0.7054	
12+ months until death			0.885	0.82		
9-12 months until death			0.880	0.71		
6-9 months until death			0.854	0.66		
3-4 months until death			0.810	0.66		
1-3 months until death			0.739	0.57		
<1month until death			0.631	0.33		

It is not possible to directly compare utility values from prior NICE melanoma technology appraisals, due to differences in measurement time points. However the

results from the coBRIM study are broadly consistent with existing melanoma appraisals.

Adverse reactions

5.4.6 Describe how adverse reactions affect HRQL.

Utility values were taken directly from the coBRIM study, and therefore any utility decrement due to adverse events whilst receiving the intervention or comparator are assumed to be captured within these results.

Health-related quality-of-life data used in cost-effectiveness analysis

5.4.7 Define what a patient experiences in the health states in terms of HRQL in the cost-effectiveness analysis.

The utilities for patients who are in PFS are taken from the coBRIM study, and therefore represents the utility of patients receiving cobimetinib + vemurafenib or vemurafenib alone for metastatic or unresectable melanoma.

Once patients enter the progressed disease state, and stop treatment with cobimetinib + vemurafenib, it is assumed their HRQoL will decline. These patients are likely to experience a worsening of symptoms, and associated QoL. In clinical practice these patients will often receive palliative and best-supportive-care.

Feedback from the ERG and Appraisal Committee during the appraisal of vemurafenib (TA269, 2012) proposed patients who remain in a progressed, but stable disease-state experience an improved utility after 5 years of survival; specifically, patient's HRQoL will increase, as their disease and symptom burden will be more consistent with the PFS state. As such their HRQoL is assumed to increase as compared to patients in early PD (<5 years), although not to the pre-progression value.

As described in section 5.4.1, limited EQ-5D-5L observations for PD were available from the coBRIM study. Results are available for a maximum of 12 weeks after end of study treatment, thus not representing patients in a prolonged stable condition.

The resulting values seen in Table 33 are not consistent with the utility values for metastatic melanoma patients in PD used in prior appraisals.

As such utility values for patients in PD, and utlity values for patients in progressed but stable disease for more than 5 years are taken from a study by Beusterien et al, (2009). This approach is consistent with the prior vemurafenib appraisal (TA269),and feedback provided by clinicians and health economists in the development of this current appraisal. The values reported in this study are 0.59 for patients in PD, and 0.77 for patients with stable progressed disease.

5.4.8 HRQL over time

See section 5.4.7 above.

5.4.9 Baseline HRQL

Baseline utility is equal to that of the PFS state, and patients remain at this utility until disease progression.

5.4.10 Adjustments to health state utility values.

Utility values for the PFS state were taken directly from patients in the coBRIM study, as such no adjustment was required. See section 5.4.2 for methods used to derive utilities from the EQ-5D-5L results of the study.

For the PD<5 years and PD≥5 years states, unadjusted utility values were taken from the literature (Beusterien, 2009). See section 5.4.7

5.4.11 Health effects found in the literature or clinical trials excluded from the cost effectiveness analysis.

None identified

5.4.12 Summary of the utility values chosen for the cost-effectiveness analysis

Table 36 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
PFS (cobimetinib + vemurafenib)	0.837 (0.004)	0.830, 0.844	5.4.1	Derived from EQ-5D-5L results directly from the coBRIM study
PFS (vemurafenib)	0.819 (0.004)	0.812, 0.827	5.4.1	
PFS (dabrafenib)	0.819 (0.004)	0.812, 0.827	5.4.1	Consistent with vemurafenib monotherapy
PD <5 years	0.590 (0.02)	0.578, 0.602	5.4.4	Limited data available for health state from coBRIM study.
PD ≥5 years	0.770 (0.02)	0.755, 0.785	5.4.4	UK standard gamble study assess melanoma health states

5.4.13 Clinical experts assessment of applicability of health state utility values

As described in section 5.4.2., Clinical and Health Economics experts were consulted on the plausibility of the utility values for the PFS health state. A preference for direct value sets as compared to mapping algorithms was expressed. However the OHE EQ-5D-5L value set for results of the coBRIM study resulted in values above the UK population norm for age 55 (average coBRIM age). Some functional weaknesses of the OHE value set were discussed.

It was determined the crosswalk values were clinically plausible and preferred. Additionally the total QALY gain of 3.034 for cobimetinib + vemurafenib was deemed appropriate and plausible.

5.5 Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

5.5.1-5.5.2 Describe how relevant cost and healthcare resource use data for England were identified.

A SLR was conducted to identify published evidence regarding the resource use and costs associated with the management and treatment of advanced melanoma. Detailed descriptions of the search strategy, search terms and abstraction methods are provided in appendix 13.

Briefly; searches of the MEDLINE® and MEDLINE® In-Process, Embase®, the Cochrane Library databases and EconLit were conducted in Ovid and limited to studies published in English between 2000 and December 2015. Search inclusion and exclusion criteria are found in Table 37.

Table 37 Cost and resource use search: inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Advanced (unresectable or metastatic) melanoma[a]	Early stage melanoma
Interventions	Not restricted by intervention	
Outcomes[b]	Direct costs (including any intervention costs, costs to the payer) Total costs Resource use Cost drivers	Indirect costs (e.g. associated with sick leave, disability)
Study design	Not restricted by study design	Economic evaluations Studies where the perspective of the costing analysis was unclear
Date restrictions	1 January 2000 to 9 December 2015	
Language restrictions	English language	Non-English languages
Publication type	Primary paper, congress abstracts	Review, editorial, letter

Of the studies, 79 met the broad inclusion criteria of the SLR (the search was not restricted by geographical location), two were considered relevant to this submission. Johnston et al., 2012 (Johnston et al., 2012) performed a retrospective observational study to assess the resource use and costs associated with patients with advanced (stage III/IV) melanoma on active treatment (treatment detail not reported) or BSC in the UK, France and Italy. Patients who presented at participating sites between 1 July 2005 and 30 June 2006 and had at least 2 months follow-up were enrolled, and their medical records from diagnosis until 1 May 2008 or death were used to calculate utilisation. Costs were estimated by multiplying unit costs from UK NHS perspective with resources utilised (cost reference year 2009). Costs associated with

hospitalisation, hospice costs and outpatient costs, both per user and per patient were reported.

A study by Vouk et al., 2014 (Vouk et al.) assessed the per-event cost and economic burden associated with managing the most common and/or severe AEs in the UK in patients with metastatic melanoma undergoing chemotherapy, targeted therapy, immunotherapy or a combination of these. An SLR was conducted to identify the AEs associated with treatment and two double-blinded Delphi panel interview cycles with four clinicians were used to estimate medical resource use associated with AE management. The cost reference year used was 2011–2012 and costs per-event, per-patient, were calculated and reported.

5.5.3 NHS reference costs or payment-by-results (PbR) tariffs

There are no NHS reference costs or payment-by-results (PbR) tariffs which are specific for cobimetinib + vemurafenib.

5.5.4 Clinical expert assessment of the applicability of the cost and healthcare resource use values available

Resource use assumptions were discussed with expert advisors. See 5.5.6 below for detail.

Intervention and comparators' costs and resource use

5.5.5 Summary of cost and associated healthcare resource use of each treatment.

The intervention and both comparators are oral medications, with fixed dosing.

The following sections detail costs and healthcare resource use for each treatment:

5.5.5.1: Drug costs

5.5.5.2: Time on treatment

5.5.5.3: Administration

5.5.5.1: Drug costs

Details of drug cost assumptions can be found in Table 38 and Table 39 below. The drug costs are presented based on their published list prices.

Table 38 Weekly drug costs as per label dosing

	According to label dose	List price	Per cycle cost (week)
Cobimetinib	60 mg (3 tablets of 20 mg) once daily for days 1 - 21 of a 28 day treatment cycle	20mg x 63 = £4275.67	£1425.22*
Vemurafenib (either in combination with cobimetinib or monotherapy)	960 mg twice daily (equivalent to a total daily dose of 1,920 mg)	240mg x 56 = £1750	£1750
Dabrafenib	150mg twice daily (equivalent to a total daily dose of 300 mg)	75mg x 28 = £1400	£1400

*during treatment periods only

The monthly cost of treatment with combination therapy according to the label dose, (taking into account the cobimetinib treatment cycle) is £12,257.26.

Dose Modification

Comparison with vemurafenib

It is possible to dose modify both cobimetinib and vemurafenib if required for patient tolerance and adverse events. The average doses taken by patients are available from the coBRIM study, and these average doses, as seen in Table 39 are incorporated into the economic model. Clinical advisors confirmed dose modifications seen in the study are likely to match those which will be seen in clinical practice.

Table 39 Weekly cobimetinib + vemurafenib drug costs at according to average dose taken in coBRIM study

	Daily dose according to label dose	Actual dose taken in coBRIM study	Per cycle cost (week)
Cobimetinib	3 tablets of 20 mg days 1 - 21 of a 28 day treatment cycle	2.602 tablets per day	£1236.07*
Vemurafenib when in combination with	8 tablets of 240mg	7.062 tablets per day	£1544.90

cobimetinib			
Vemurafenib monotherapy	8 tablets of 240mg	6.99 tablets per day	£1528.96

*during treatment periods only

The monthly cost of treatment with combination therapy according to the dose taken in the coBRIM study is £10,748.60.
The monthly cost of treatment with vemurafenib monotherapy according to the dose taken in the coBRIM study is £6625.49.

These costs exclude a confidential PAS which exists for vemurafenib (as referenced in TA269). Please see appendix 14 for details.

Comparison with Dabrafenib

In the absence of dose modification data for dabrafenib, it is assumed patients receive 100% of the dabrafenib dose, as per the label dose. The monthly cost of treatment with dabrafenib is £6066.67. This is consistent with the approach taken in the recent pembrolizumab technology appraisal (TA366 2015)

Drug wastage

The intervention and both comparators are oral medications. Patients are dispensed their medication monthly, with a quantity taking into account any specific dose modifications. As such no drug wastage is assumed for either the intervention or the comparators.

5.5.5.2: Time on Treatment

Cobimetinib + vemurafenib, and veumrafenib monotherapy

The licensed duration of treatment for cobimetinib and vemurafenib (in combination or as monotherapy) is until disease progression or until unacceptable toxicity. Results from the coBRIM study show the average treatment duration is shorter than PFS, indicating a proportion of patients discontinue treatment prior to disease progression, for reasons such as adverse events. To incorporate this disparity between treatment duration and PFS, parametric regression functions were fitted to the discontinuation KM curves for each treatment, such that treatment duration could

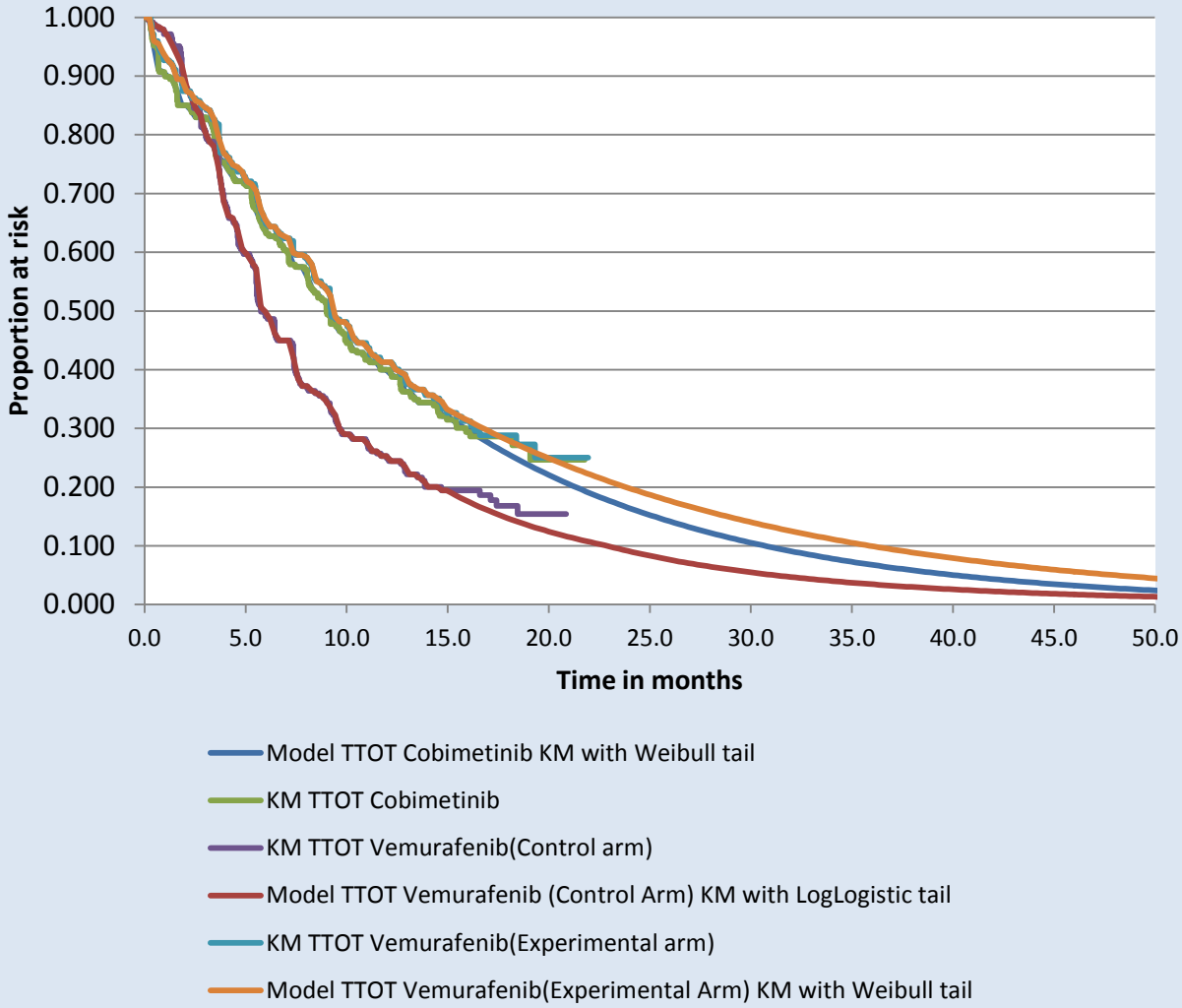
be estimated beyond the trial period. Visual assessment of the curves determined the parametric distributions were a poor fit for the beginning of the KM. As such the approach taken was KM with parametric tail fitted.

Assessment of the AIC and BIC values, determined the Weibull distribution was the best fit for both cobimetinib and vemurafenib in the experimental arm. The Log-Logistic distribution was the best fit to the vemurafenib discontinuation KM in the comparator arm. To allow application of the tails at consistent time points, the time at which 20% of patients were still at risk in the lower curve was chosen. This was month 15, as such parametric tails were applied from month 15 in both the intervention and comparator arms. Results are shown in Table 40 and Figure 26 below.

Table 40 Mean and median time on treatment from coBRIM study

	Cobimetinib + vemurafenib	**Vemurafenib**
Mean time (months)	[redacted]	[redacted]
Median time (months)	[redacted]	[redacted]

Figure 26 Time on treatment distributions for experimental and control arm of coBRIM study



Dabrafenib

Dabrafenib is licensed for treatment until disease progression or unacceptable toxicity. In the absence of available data on time to treatment discontinuation with dabrafenib, PFS will be used as a proxy for time on treatment results for dabrafenib.

For the indirect comparison of the intervention vs. dabrafenib, PFS is also used as a proxy for TOT for cobimetinib + vemurafenib. Should TOT have been used for the intervention and PFS for dabrafenib, this could overestimate the costs of dabrafenib, and underestimate the costs of the intervention.

5.5.5.3: Administration and healthcare resource use

Consistent with the approaches taken in the prior vemurafenib and dabrafenib appraisals (TA269, 2012; TA321, 2014) a pharmacy charge of £13 was applied to the first and all subsequent 28 day cycles of the intervention and both comparators.

The intervention and comparators are only licensed for use in patients who are BRAF V600 mutation positive. BRAF mutation testing is part of routine management for patients with advanced melanoma in the UK, therefore is not considered an additional cost or resource burden to the system. However as per the prior vemurafenib technology appraisal (TA269, 2012) a cost of £95 per test is incorporated into the model. As this cost is applied to both the intervention and all comparators, this does not have incremental effect.

Health-state unit costs and resource use

5.5.6 Summarise and tabulate the costs included in each health state

Specific UK costs and resource use data for the relevant health states were not available for the intervention. The SLR described in section 5.5.2 identified one key publication providing resource utilisation data for the scope population, the MELODY study (Johnston, 2012). Results from this study have been used in prior technology appraisals, including TA269 2012; TA268 2012; TA319 2014; TA357 2015 and TA366 2015. Consistent with these prior appraisals, and following advice from clinical experts, a monthly cost of £378 (£87 per week) is assumed for patients in PFS.

Feedback from the ERG assigned to the vemurafenib NICE appraisal (TA269, 2012) suggested patients remaining in the progressed state for 2+ years would require reduced monitoring as they remain in a long-term, stable condition. The proposed monitoring schedule and costs (referencing the 2014-15 HRG costs and PSSRU Unit Costs of Health & Social Care 2015) can be found in Table 41 below.

Table 41 ERG previously proposed health states costs

Health states	Items	Unit Value	Quantity	Reference in submission
PFS	BSC	£378 / month £87.23 / week	12	5.5.6
PD year 1	BSC	£378 / month	12	5.5.6

		£87.23 / week		
PD years 2-3	CT scan	£92 / scan	3.5	HRG 2014-15
	Medical oncologist outpatients	£158.54 / visit	3.5	HRG 2014-15
	GP visit	£44 / visit	4	PSSRU 2015
	Total	£1052.89 / year £20.25 / week		
PD years 4-6	CT scan	£92 / scan	2	HRG 2014-15
	Medical oncologist outpatients	£158.54 / visit	2	HRG 2014-15
	GP visit	£44 / visit	3	PSSRU 2015
	Total	£633.08 / year £12.17 / week		
PD years 6+	CT scan	£92 / scan	1	HRG 2014-15
	Medical oncologist outpatients	£158.54 / visit	1	HRG 2014-15
	GP visit	£44 / visit	2	PSSRU 2015
	Total	£338.54 / year £6.51 / week		

These proposed costs were discussed with expert advisors (see section 5.5.4). Whilst the monitoring schedule was agreed to be reasonable, they advised due to the changes in 2nd line treatment options over recent years, it was likely patients who progress (even if stable) would receive subsequent anti-cancer therapy – see section 5.5.2.

Due to this uncertainty a conservative approach was taken, and consistent resource use cost was applied throughout time (Table 42 below).

Table 42 Health state resource use costs applied in model

Health states	Items	Unit Value	Quantity	Reference in submission
PFS	BSC	£378 / month £87.23 / week	12	5.5.6
PD	BSC	£378 / month £87.23 / week	12	5.5.6

Adverse reaction unit costs and resource use

5.5.7 Summarise and tabulate the costs for each adverse reaction listed in section 4.12

The incidence of AEs for cobimetinib + vemurafenib, and vemurafenib alone were obtained from the coBRIM study. AEs of grades 3 or 4, at an incidence of 3% or more, were considered to have a significant impact on resource use, and were incorporated into the economic model. The AEs included, and unit costs incorporated into the model, can be found in Table 43 below.

Unit costs were derived from prior melanoma NICE technology appraisals or from relevant HRG reference costs 2014-15. The SLR reported in section 5.5.2 identified one paper which reported cost burden of AEs during the treatment of melanoma in the UK (Vouk, 2014). However the study was not specific to the intervention or comparators. As such it was considered more robust to utilise HRG reference costs from 2014-15, for AEs specific to the intervention and comparators.

Following discussion with melanoma clinical experts, grade 3/4 liver function test abnormalities (alanine aminotransferase increase, aspartate aminotransferase increase, gamma-glutamyltransferase increase, blood alkaline phosphatase increase, blood creatine phosphokinase increase) were costed as an additional out-patient visit to Medical Oncology. Clinical experts advised these patients would not be referred to hepatology, and around 20% of patients who experience grade 3/4 liver function test abnormalities would be treated by their Medical Oncologist at an additional clinic visit.

Incorporating the AEs and costs from Table 43 into the economic model, resulted in a weekly AE cost of £3.20 for cobimetinib + vemurafenib, and £3.90 for vemurafenib monotherapy. The higher AE treatment cost with vemurafenib alone was predominantly driven by the greater incidence of squamous cell carcinoma of the skin, as compared to cobimetinib + vemurafenib.

Published dabrafenib safety data to the equivalent level of detail was not available for incorporation into the model. As such the AE costs for the comparator dabrafenib were assumed the same as the lower cobimetinib + vemurafenib cost.

Table 43 List of adverse reactions and summary of costs in the economic model

Adverse reactions	Items	Value	Reference in submission
Liver function test abnormality* Average estimate	Outpatient cost, % No treatment, % Total	£158.54, 20% £0, 90% £31.71	HRG service code 370, medical oncology
Arthralgia	Outpatient cost	£139.52	HRG service code 191, pain management
Basel cell carcinoma	Other costs	£198.66	JC41Z: outpatient major skin procedure
Diarrhoea	Inpatient cost, %	£838.46, 50%	TA366 2015
	Outpatient cost, %	£144.05, 50%	TA366 2015
	Average per patient	£491.26	TA366 2015
Fatigue	Inpatient cost, %	£596.38, 10%	TA366 2015
	Outpatient cost, %	£156.84, 90%	TA366 2015
	Average per patient	£200.79	TA366 2015
Hypertension		£287.04	EB04Z: outpatient procedure
Hyponatraemia	Cost assumed £0	Cost assumed £0	TA366 2015
Keratoacanthoma	Other costs	£198.66	JC41Z: outpatient major skin procedure
Pain in extremity	Outpatient cost	£139.52	HRG service code 191, pain management
Rash		£137.31	TA269 2012
Rash-maculo popular		£137.31	TA269 2012
Squamous cell carcinoma of skin	Other costs	£198.66	JC41Z: outpatient major skin procedure

* Alanine aminotransferase increase, aspartate aminotransferase increase, gamma-glutamyltransferase increase, blood alkaline phosphatase increase, blood creatine phosphokinase increase

Miscellaneous unit costs and resource use

5.5.8 Describe and tabulate any additional costs and healthcare resource use that have not been covered elsewhere

As described in section 5.2.2, the costs associated with post-progression treatments are not included in the model due to the lack of available data. Given the similarity in use of follow-up treatments across arms of the coBRIM study, this is not anticipated to have a significant impact on cost-effectinvess results (Table 27).

This approach is consistent with prior melanoma appraisals for first-line therapies (TA269 2012; TA319 2014; TA321 2014; TA366 2015).

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

5.6.1 Tabulate all variables included in the cost-effectiveness analysis

Please see Table 44 below.

5.6.2 For the base-case de novo analysis the company should ensure that the cost-effectiveness analysis reflects the NICE reference case as closely as possible.

The base-case cost-effectiveness analysis reflects the NICE reference case.

Table 44 Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General parameters			
Patient age	55 years (Table 14)	Fixed	4.5.2
Discount rate (costs)	3.5%	Fixed	5.2.3
Discount rate (efficacy)	3.5%	Fixed	5.2.3
Time horizon	30 years	Fixed	5.2.3
Utility values			
PFS cobimetinib + vemurafenib	0.837 (Table 36)	See Table 36 gamma distribution	5.4.12
PFS vemurafenib	0.819 (Table 36)	See Table 36 gamma distribution	5.4.12
PFS dabrafenib	0.819 (Table 36)	See Table 36 gamma distribution	5.4.12
PD ≥5 years	0.770 (Table 36)	See Table 36 gamma distribution	5.4.12
PD< 5 years combimetinib + vemurafenib	0.590 (Table 36)	See Table 36 gamma distribution	5.4.12
PD< 5 years vemurafenib	0.590 (Table 36)	See Table 36 gamma distribution	5.4.12
Parametric survival curves			
PFS cobimetinib + vemurafenib	See Figure 16 and Figure 25	Multivariate normal distribution	5.3
PFS vemurafenib	See Figure 16 and Figure 25	Multivariate normal distribution	5.3
PFS AFT dabrafenib vs. cobimetinib + vemurafenib	0.599 (Table 22)	Log-normal distribution	4.10
PFS dabrafenib	See Figure 16 and Figure 25	Multivariate normal distribution	5.3
OS cobimetinib + vemurafenib	See Figure 23 and Figure 25	Multivariate normal distribution	5.3
OS vemurafenib	See Figure 23 and Figure 25	Multivariate normal distribution	5.3
OS AFT dabrafenib vs. cobimetinib + vemurafenib	See 0.635 (Table 21)	Log-normal distribution	4.10
OS dabrafenib	See Figure 23 and Figure 25	Multivariate normal distribution	5.3
Parametric survival tail for treatment duration			
TOT cobimetinib +	See Figure 26	KM, followed by Multivariate normal	5.5.5.2

vemurafenib tail		distribution tail	
TOT vemurafenib tail	See Figure 26	KM, followed by Multivariate normal distribution tail	5.5.5.2
TOT dabrafenib tail	See Figure 26	KM, followed by Multivariate normal distribution tail	5.5.5.2
Drug dose assumptions			
Cobimetinib	See Table 39	Fixed	5.5.5.1
Vemurafenib (when in combination)	See Table 39	Fixed	5.5.5.1
Vemurafenib (monotherapy)	See Table 39	Fixed	5.5.5.1
Dabrafenib	As per lable	Fixed	5.5.5.1
Treatment costs			
Cobimetinib	£4275.67 / pack (list price)	Fixed	5.5.5.1
vemurafenib	£1750 / pack (list price)	Fixed	5.5.5.1
dabrafenib	£1400 / pack (list price)	Fixed	5.5.5.1
Administration costs	£13	SE=0.0775 Log-normal distribution	
Health state costs			
Cost of PFS	£87.23 / week (Table 42)	SE=0.3876 Log-normal distribution	5.5.6
Cost of PD	£87.23 / week (Table 42)	SE=0.3876 Log-normal distribution	5.5.6
Adverse event			
Individual AEs costs	Table 43	Log-normal distribution	5.5.7
Average AE cost cobimetinib + vemurafenib	£3.20 / week	Log-normal distribution	5.5.7
Average AE cost vemurafenib	£3.90 / week	Log-normal distribution	5.5.7
Average AE cost dabrafenib (equivalent to lower weekly cost from coBRIM)	£3.20 / week	SE=0.3466 (compared to cobimetinib + vemurafenib AE costs) Log-normal distribution	5.5.7

Assumptions

5.6.3 Provide a list of all assumptions used in the de novo economic model and justify each assumption.

The de novo model used a range of assumptions, details of which can be found throughout section 5 of this submission. Key assumptions are detailed in Table 45 below.

Table 45 Key assumptions used in economic model

Area	Assumption	Justification
Time horizon	30 years	Consistent with prior melanoma appraisals and appropriate for average age of patients in the model.
Clinical efficacy and safety	Efficacy and safety results for cobimetinib + vemurafenib seen in the coBRIM study are transferable to UK population	The coBRIM study included UK patients. Expert clinical advice suggests the outcomes seen from the study are expected in UK patients.
HRQoL	Use of EQ-5D-5L results directly from the coBRIM study, and valued using the crosswalk algorithm is appropriate to obtain utility values	HRQoL results taken directly from patients receiveing cobimetinib + vemurafenib, and crosswalk value set independently validated.
	Patients in progressed but stable state ≥5 years have improved HRQoL compared to patients <5 years	ERG feedback from previous appraisals (see section 5.4)
Dose	Patients will receive reduced treatment dose for both cobimetinib and vemurafenib, in	Dose modifications due to treatment tolerance are permitted within the licensed doses of both

	line with the average doses from the coBRIM study.	cobimetinib and vemurafenib.
Treatment duration	Treatment duration is based on time on treatment results of the coBRIM study rather than assuming all patients receive treatment until progression.	Results from coBRIM suggest some patients may stop treatment due to tolerability and AEs, as opposed to progression.
Resource use	As per section 5.5.5	Assumptions based on prior melanoma appraisals, and feedback received from ERG appraisal reviews.
Indirect treatment comparison	Various assumptions	See section 4.10

5.7 Base-case results

Base-case incremental cost effectiveness analysis results

5.7.1-2 Provide results of the analysis.

Base-case results of the economic model are presented below. These results do not include application of the PAS for vemurafenib (either in combination with cobimetinib, or as monotherapy), or the comparator dabrafenib.

Cobimetinib + vemurafenib resulted in a QALY gain of 3.034, a life-year gain of 4.015 and total cost of £163,974. This compares to 2.489 QALY gain, 3.392 life-year gain and £81,984 total costs for vemurafenib monotherapy. The resulting ICER for cobimetinib + vemurafenib compared to vemurafenib is £150,514.

In the indirect comparison to dabrafenib, PFS was used as a proxy for time on treatment. As such, total costs for cobimetinib + vemurafenib differ to those in the direct comparison, which utilitised time on treatment results. When comparing to

dabrafenib, cobimetinib + vemurafenib resulted in a QALY gain of 3.034, a life-year gain of 4.015 and total cost of £208,047. This compares to 2.417 QALY gain, 3.281 life-year gain and £78,392 total costs for dabrafenib monotherapy. The resulting ICER for cobimetinib + vemurafenib compared to dabrafenib is £209,942

Table 46 Base-case results, (list prices), for direct treatment comparison (actual TOT used)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Cobimetinib + vemurafenib	£163,974	4.015	3.034					
Vemurafenib monotherapy	£81,984	3.392	2.489	£81,990	0.622	0.545	£150,514	£150,514
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 47 Base-case results, (list prices) for indirect treatment comparison (PFS as surrogate for TOT)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Cobimetinib + vemurafenib	£208,047	4.015	3.034					
Dabrafenib	£78,392	3.281	2.417	£129,655	0.733	0.618	£209,942	£209,942
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Clinical outcomes from the model

5.7.3 Comparison of model outcomes with clinical trial outcomes

The coBRIM study allowed direct comparison between the intervention and one appraisal comparator - vemurafenib. As shown in The BREAK-3 study (Hauschild 2013) is the phase III, licencing trial for dabrafenib, which compared treatment with dabrafenib to dacarbazine. Table 48 indicates there is some divergence between the model results and clinical results from this study, specifically for OS. These results should be interpreted with caution as the follow-up results for BREAK-3 are only published via an abstract, and the median follow-up reported was only 15.2 months for the dabrafenib arm.

Table 48, the economic model results are highly comparable with corresponding clinical data. The coBRIM study did not allow cross-over, and therefore represents an unconfounded basis from which to project long-term clinical benefit. See section 4.13 for a discussion of the applicability of coBRIM results to the UK population.

The BREAK-3 study (Hauschild 2013) is the phase III, licencing trial for dabrafenib, which compared treatment with dabrafenib to dacarbazine. Table 48 indicates there is some divergence between the model results and clinical results from this study, specifically for OS. These results should be interpreted with caution as the follow-up results for BREAK-3 are only published via an abstract, and the median follow-up reported was only 15.2 months for the dabrafenib arm.

Table 48 Summary of model results compared with clinical data

Outcome	Clinical trial result (months)	Model result (months)
Results from coBRIM study		
Median PFS cobimetinib + vemurafenib	12.3	11.5
Median PFS vemurafenib	7.2	7.1
Median OS cobimetinib + vemurafenib	22.3	23.9
Median OS vemurafenib	17.4	17.0
Results from BREAK-3 study		
Median PFS dabrafenib	6.9	6.9
Median OS dabrafenib	18.2	15.4

5.7.4 Provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying 1 for each comparator.

Figure 27, Figure 28, and Figure 29 illustrate the movement of patients through the model health states, over time. From these figures it can be seen patients spend a greater amount of time in the PFS state, and experience longer OS when receiving cobimetinib + vemurafenib, as compared to vemurafenib or dabrafenib alone.
Figure 30 shows aggregated results for all health states for the direct comparison of cobimetinib + vemurafenib, vs vemurafenib.

Figure 27 Markov trace for health states over time: cobimetinib + vemurafenib

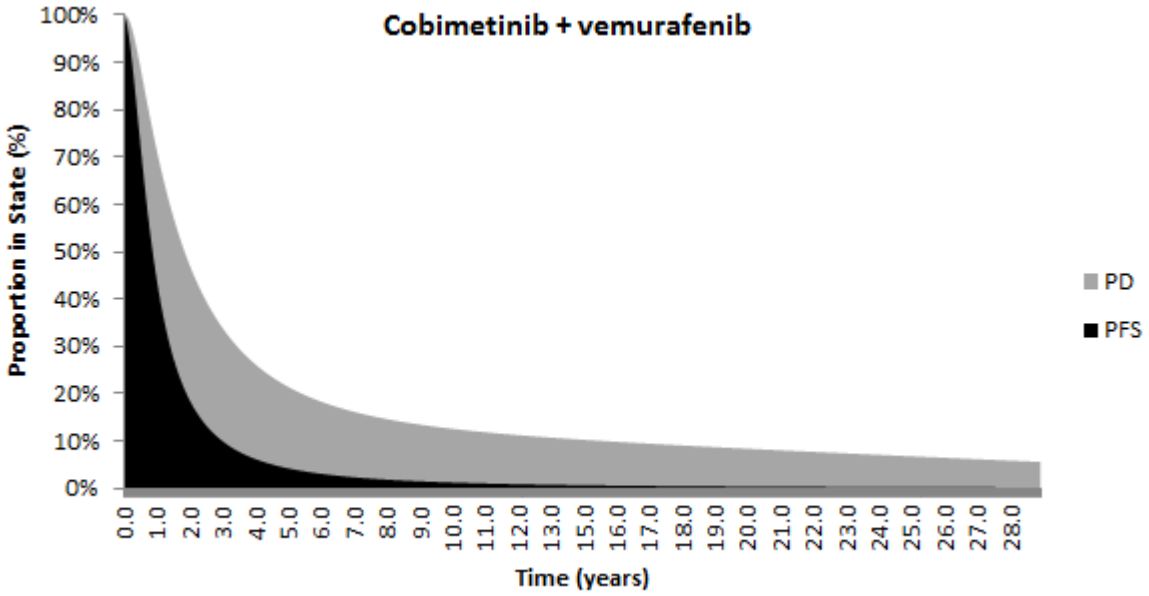


Figure 28 Markov trace for health states over time: vemurafenib monotherapy

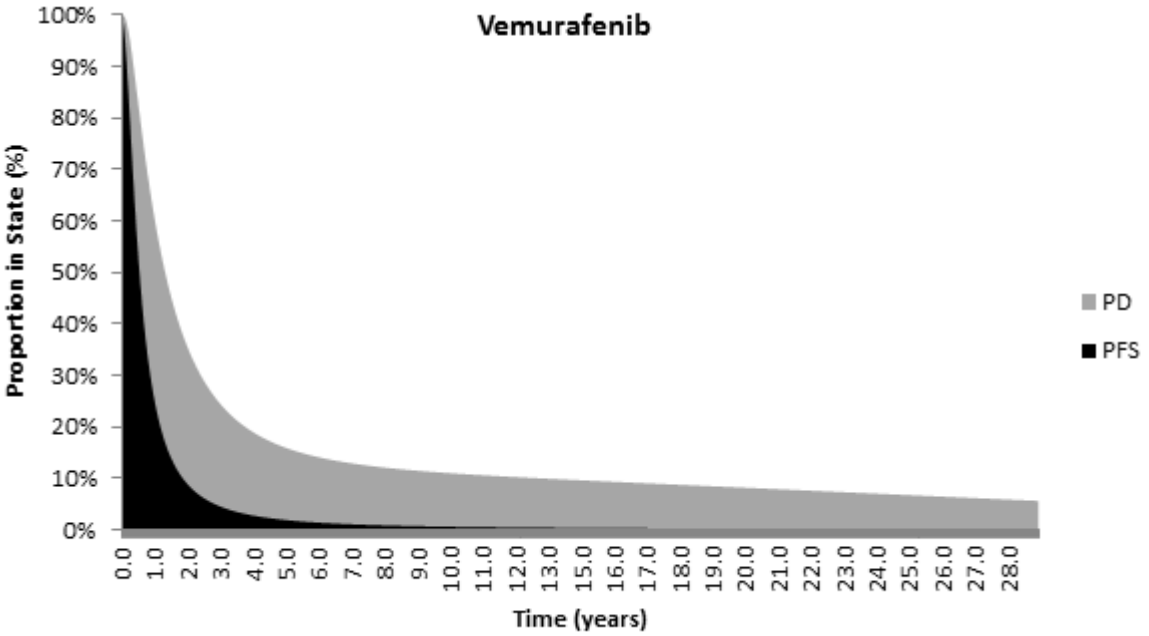


Figure 29 Markov trace for health states over time: dabrafenib monotherapy

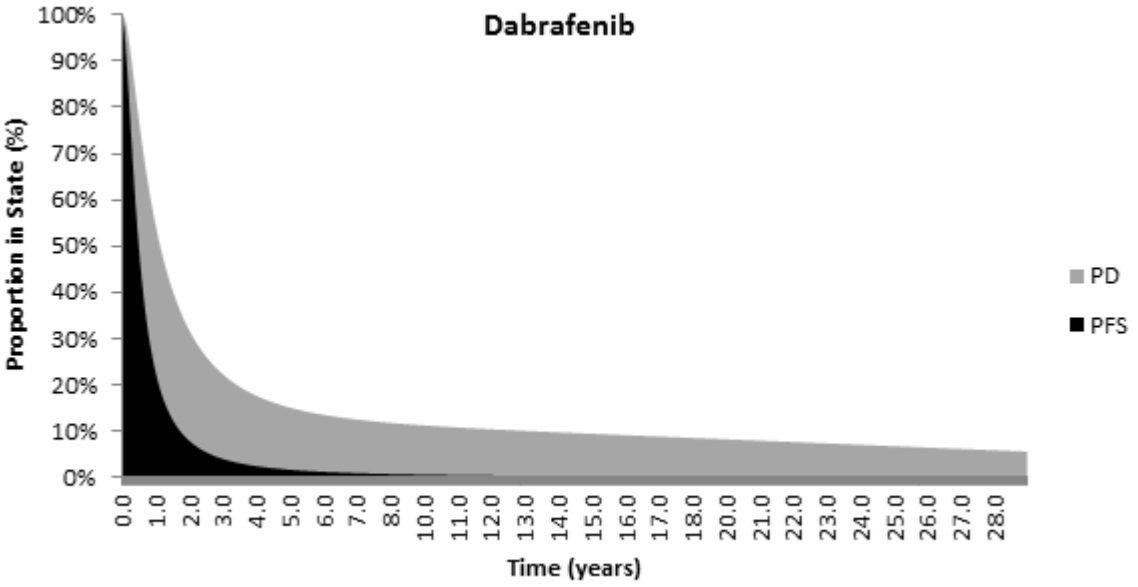
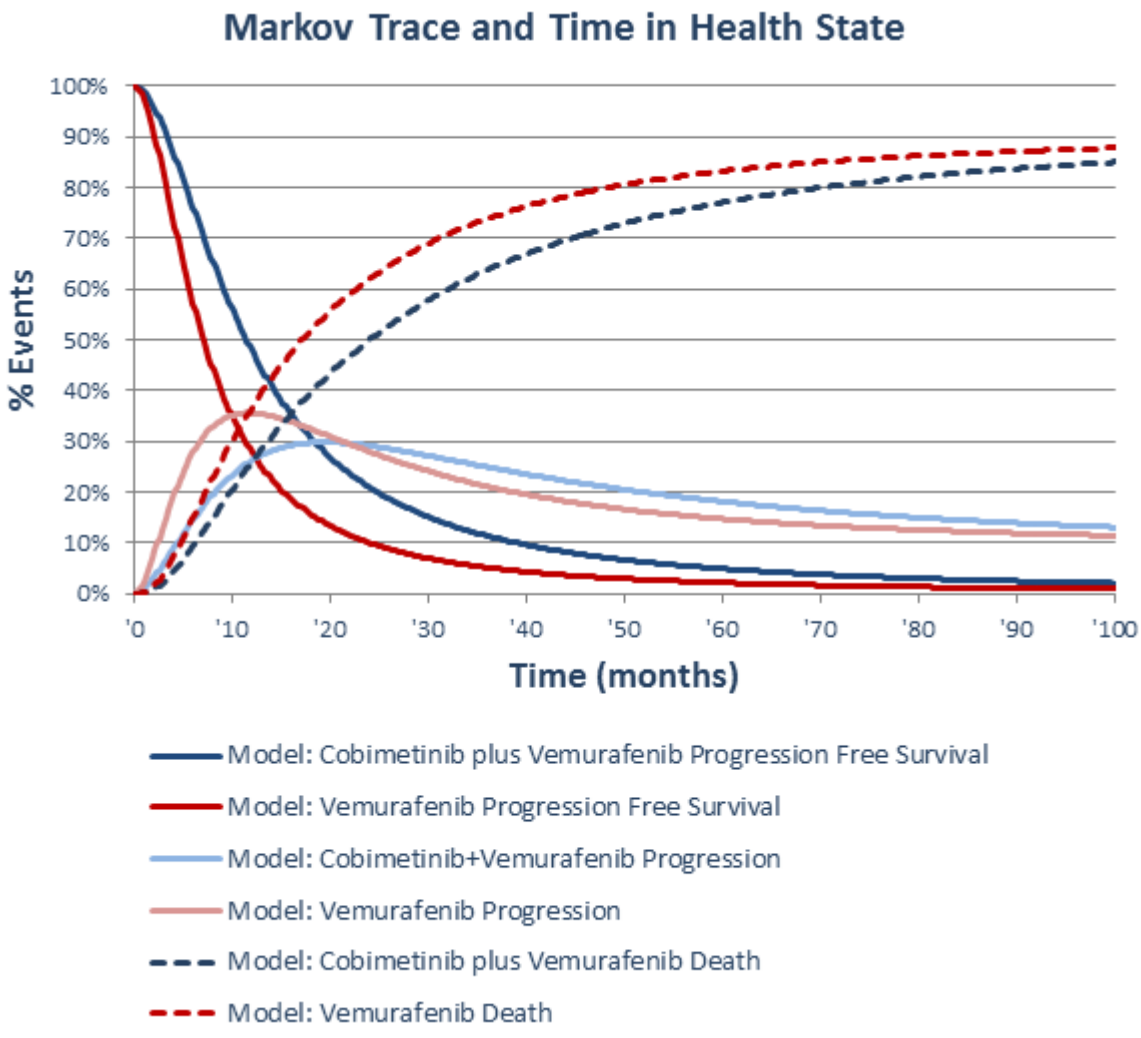


Figure 30 Markov trace: combined for results from coBRIM study

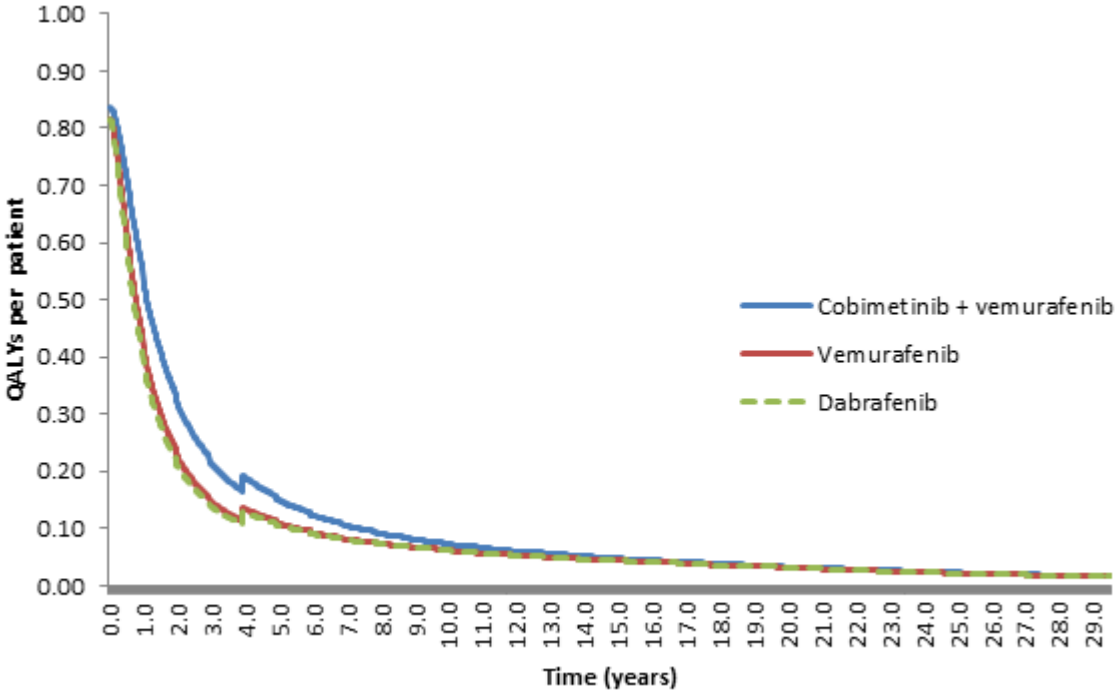


5.7.5 Provide details of how the model assumes QALYs accrued over time.

The utility of patients (measured in QALYs) in the years since their treatment initiation (cobimetinib + vemurafenib, vemurafenib or dabrafenib) is shown in Figure 31 below. As expected the patients' utility gradually decreases over time, with cobimetinib + vemurafenib providing a greater utility for patients as compared to vemurafenib or dabrafenib alone.

The small increase in utility seen at year 5 since diagnosis is expected, as the utility for patients in stable disease for ≥5 years increases (see section 5.4 for explanation and rationale).

Figure 31 Utility per patient, per year since treatment initiation for cobimetinib + vemurafenib; vemurafenib and dabrafenib



Disaggregated results of the base case incremental cost effectiveness analysis

5.7.6 Provide details of the disaggregated results

Results of the base-case analysis are presented below. Results are presented as pairwise comparisons of the intervention vs. the two comparators.

The QALY and life-year gains are shown in Table 49 and Table 51 for the comparison of cobimetinib + vemurafenib to vemurafenib; and Table 50 and Table 52 for the comparison of cobimetinib + vemurafenib to dabrafenib. The results demonstrate an incremental gain for both QALYs and life-years for patients receiving cobimetinib + vemurafenib, vs. both comparators.

Table 49 Summary of QALY gain by health state: cobimetinib + vemurafenib vs. vemurafenib

Health state	QALYs: cobimetinib + vemurafenib	QALYs: vemurafenib	Increment	% absolute increment*
PFS	1.263	0.790	0.473	87%
PD	1.771	1.699	0.071	13%
Total	**3.034**	**2.489**	**0.545**	**100%**

*results rounded

Table 50 Summary of QALY gain by health state: cobimetinib + vemurafenib vs. dabrafenib

Health state	QALYs: cobimetinib + vemurafenib	QALYs: dabrafenib	Increment	% absolute increment*
PFS	1.263	0.769	0.494	80%
PD	1.771	1.647	0.124	20%
Total	**3.034**	**2.417**	**0.618**	**100%**

*results rounded

Table 51 Summary of life-year gain by health state: cobimetinib + vemurafenib vs. vemurafenib

Health state	Life-years: cobimetinib + vemurafenib	Life-years: vemurafenib	Increment	% absolute increment*
PFS	1.509	0.965	0.545	88%
PD	2.505	2.428	0.078	12%
Total	**4.015**	**3.392**	**0.622**	**100%**

*results rounded

Table 52 Summary of life-year gain by health state: cobimetinib + vemurafenib vs. dabrafenib

Health state	Life-years: cobimetinib + vemurafenib	Life-years: dabrafenib	Increment	% absolute increment*
PFS	1.509	0.939	0.570	78%
PD	2.505	2.342	0.163	22%
Total	**4.015**	**3.281**	**0.733**	**100%**

*results rounded

A break-down of the difference in costs can be found below. Table 53 and Table 54 show the two comparisons by health states, and Table 55 and Table 56 present the results by resource and category use. Treatment costs are based on the published list price of therapies.

A difference for cobimetinib + vemurafenib costs is seen between Table 53 and Table 54, and also between Table 55 and Table 56. This difference in costs is due to use of TOT data from the coBRIM study for the direct comparison with vemurafenib monotherapy. These data were not available for dabrafenib, as such PFS was used as a surrogate for TOT. For the indirect comparison with dabrafenib, PFS was also used as a proxy for TOT for cobimetinib + vemurafenib. Should TOT have been used for the intervention and PFS for dabrafenib, this could overestimate the costs of dabrafenib, and underestimate the costs of the intervention (see section 5.5.5.2).

Table 53 Summary of costs by health state: cobimetinib + vemurafenib vs. vemurafenib

Health state	Costs: cobimetinib + vemurafenib	Costs: vemurafenib	Increment	% absolute increment*
PFS	£158,543	£76,524	£82,019	100%
PD	£5,431	£5,460	-£29	0%
Total	**£163,974**	**£81,984**	**£81,990**	**100%**

*results rounded

Table 54 Summary of costs by health state: cobimetinib + vemurafenib vs. dabrafenib

Health state	Costs: cobimetinib + vemurafenib	Costs: Dabrafenib	Increment	% absolute increment*
PFS	£202,616	£73,318	£126,299	100%
PD	£5,431	£5,075	£356	0%
Total	**£208,047**	**£78,392**	**£129,655**	**100%**

*results rounded

Table 55 Summary of predicted resource use by category of cost: cobimetinib + vemurafenib vs. vemurafenib

Item	Costs: cobimetinib + vemurafenib	Costs: vemurafenib	Increment	% absolute increment*
Treatment cost	£151,209	£71,699	£79,510	97%
Diagnostic cost	£95	£95	£0	0%
Admin costs	£188	£157	£31	0%
Adverse events	£181	£183	-£2	0%
Supportive care (PFS)	£6,870	£4,390	£2,480	3%
Supportive care (PD)	£5,431	£5,460	-£29	0%
Total	**£163,974**	**£81,984**	**£81,990**	**100%**

*results rounded

Table 56 Summary of predicted resource use by category of cost: cobimetinib + vemurafenib vs. dabrafenib

Item	Costs: cobimetinib + vemurafenib	Costs: dabrafenib	Increment	% absolute increment*
Treatment cost	£195,138	£68,625	£126,513	98%
Diagnostic cost	£95	£95	£0	0%
Admin costs	£261	£164	£97	0%
Adverse events	£252	£157	£95	0%
Supportive care (PFS)	£6,870	£4,276	£2,594	2%
Supportive care (PD)	£5,431	£5,075	£356	0%
Total	**£208,047**	**£78,392**	**£129,655**	**100%**

*results rounded

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

5.8.1 – 5.8.4 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted using 1000 samples, to assess uncertainty surrounding variables. The distributions and sources to estimate parameters can be found in section 5.6. Analyses are based on the list price of all treatments: See appendix 14 for details of results with PASs included.

Results of the PSA compared to deterministic results are presented in Table 57 and Table 58. Results of the PSA are similar to base case results from the deterministic analyses, for both the direct and indirect comparisons.

Table 57 Mean results of PSA compared to base case (list prices) for cobimetinib + vemurafenib vs. vemurafenib

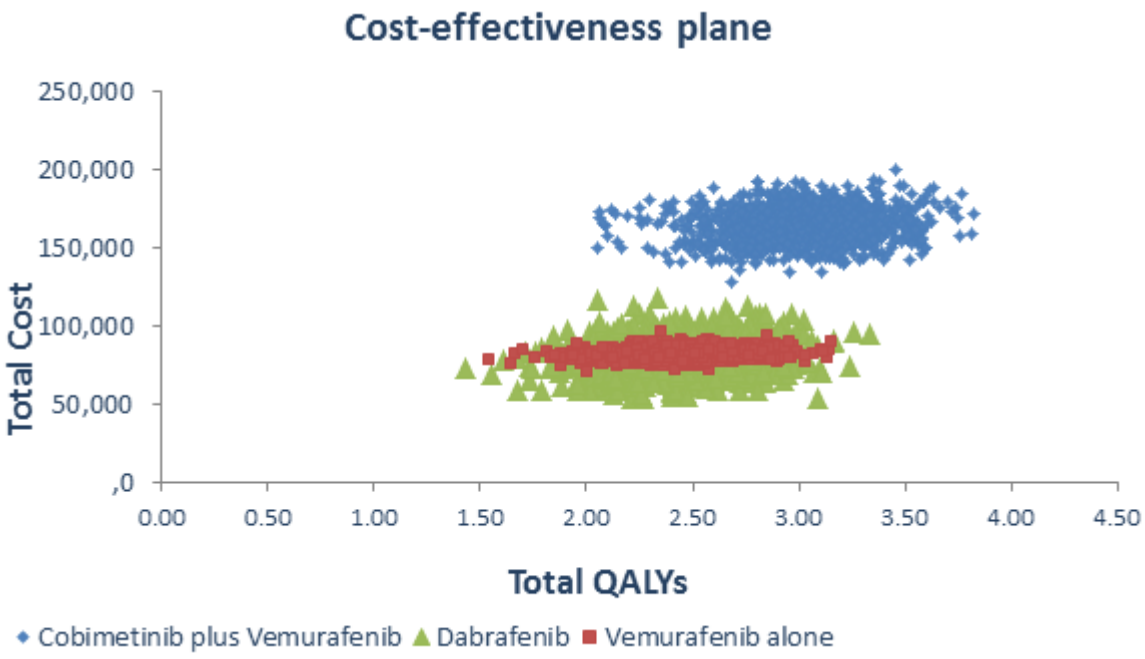
	Costs		QALYs		ICER	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
Cobimetinib + vemurafenib	£163,974	£164,636	3.034	3.028	£150,514	£151,668
Vemurafenib	£81,984	£81,615	2.489	2.480		

Table 58 Mean results of PSA compared to base case (list prices) for cobimetinib + vemurafenib vs. dabfrafenib

	Costs		QALYs		ICER	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
Cobimetinib + vemurafenib	£208,047	£210,076	3.034	3.028	£209,942	£215,264
dabrafenib	£78,392	£79,472	2.417	2.421		

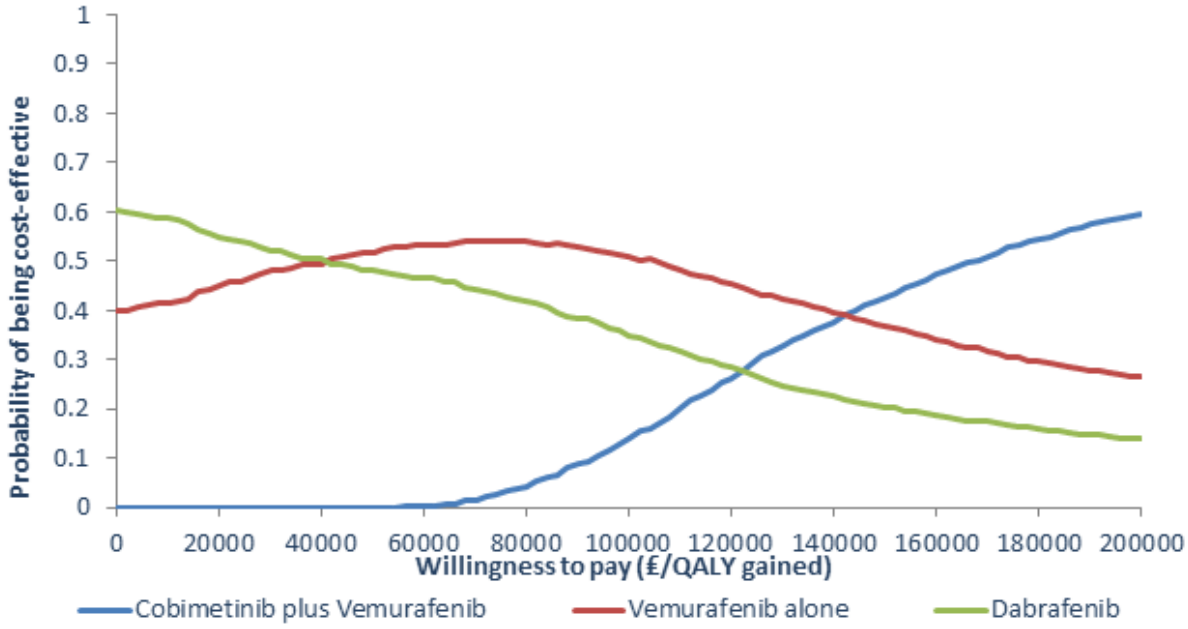
The scatterplot in Figure 32 below presents the PSA iterations. Whilst there is variation from the simulations, the cobimetinib + vemurafenib plots do not overlap with either vemurafenib or dabrafenib in terms of QALYs or costs. These results indicate none of the 1000 simulations resulted in a lower QALY gain for cobimetinib + vemurafenib compared to vemurafenib or dabrafenib.

Figure 32 Scatterplot of PSA results for cost effectiveness plane



The cost-effectiveness acceptability curves can be seen in Figure 33. These results demonstrate there is a 0% probability of cobimetinib + vemurafenib being cost effective at the thresholds £30,000 or £50,000 / QALY.

Figure 33 Cost-effectiveness acceptability curve, excluding PASs



Deterministic sensitivity analysis

5.8.5 – 5.8.7 Deterministic sensitivity analysis

Deterministic sensitivity analysis was conducted varying the following parameters:

- Weekly cost of cobimetinib ± 50%
- Weekly cost of vemurafenib (when in combination with cobimetinib) ± 50%
- Supportive costs PFS ± 50%
- Utility PFS health state – cobimetinib + vemurafenib: 25th percentile and maximum value
- Utility PFS health state – vemurafenib: 25th percentile and maximum value
- Utility progression health state ± minimum and maximum values

As seen above in section 5.7.6, these inputs are the parameters with the greatest impact on percentage increment in costs or QALYs, thus having the greatest impact on the resulting ICER.

Results for the deterministic sensitivity analysis are found in Figure 34 and Table 59 below. Vemurafenib results included in this figure are when in combination with cobimetinib, only.

The results show the model is sensitive to these parameter inputs. Scenario analysis below further explores this.

Figure 34 Univariate Sensitivity Analysis (red = lower value ; blue = upper value)

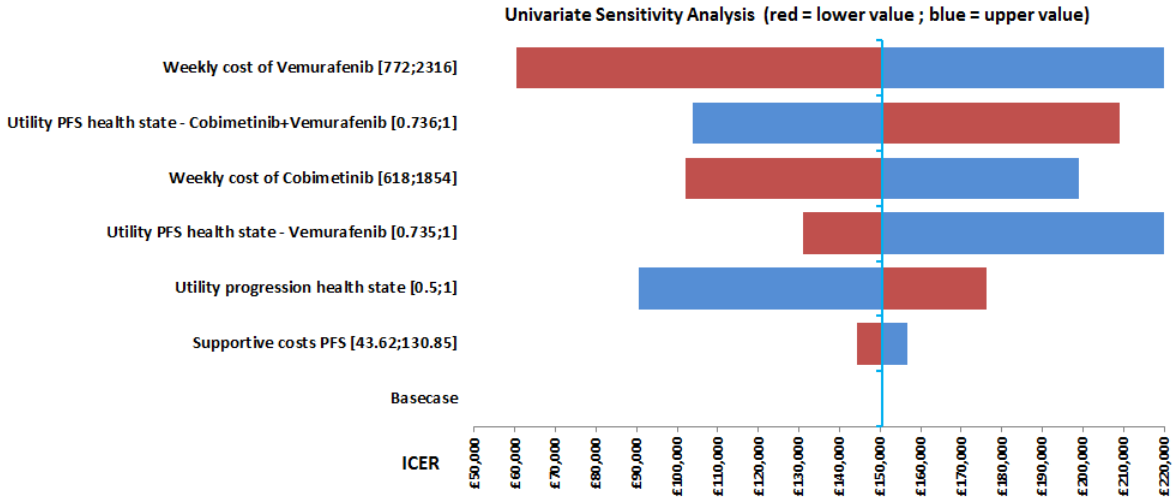


Table 59 Univariate sensitivity analysis ICER ranges

Variable	Range (% of base case)	Resulting ICER using lower value	Resulting ICER using higher
Weekly cost cobimetinib	±50%	£101,933	£199,082
Weekly cost of vemurafenib	±50%	£60,248	£240,568
Supportive costs (PFS)	±50%	£144,209	£156,820
Utility PFS cobimetinib + vemurafenib	25th percentile: 0.736 Upper:1	£209,002	£103,686
Utility PFS vemurafenib	25th percentile 0.735 Upper:1	£131,025	£221,505
Utility PD	Lower :0.5 Upper:1	£176,090	£90,579

Scenario analysis

5.8.8 – 5.8.9 Scenario analysis

Scenario analyses were conducted to assess uncertainty around structural assumptions of the model. Results are shown in Table 60 for the following scenarios exploring parameter changes:

- Alternative PFS and OS parametric distributions
- Utilities
    - Alternative health state utilities using the OHE method for EQ-5D-5L valuation
    - Alternative health states utilities using one PD utility value
- Dose / treatment duration assumptions
    - Alternative TOT parametric distributions
    - PFS as a proxy for TOT for cobimetinib + vemurafenib vs. vemurafenib
    - Dosing as per label for cobimetinib + vemurafenib vs. vemurafenib
- Discount rate (1.5% rather than 3.5%)
- Time horizons of 10 and 20 years
- Drug costs of £0 for cobimetinib or vemurafenib

The scenarios indicate without PASs there are no conditions at which the ICER is below the acceptable threshold.

Table 60 Resulting ICER vs vemurafenib or dabrafenib from scenario analyses (List prices)

Scenario	Base case	Analyses	ICER intervention vs. vemurafenib	ICER intervention vs. dabrafenib
Base case	n/a	n/a	£150,514	£209,942
	OS parametric distribution			
1	LogNormal	Exponential	£161,902	£219,912
2		Weibull	£229,890	£269,146

3		LogLogisitic	£175,592	£212,255
4		Gompertz	£253,766	£269,898
5		Gamma	£217,135	£262,084
	PFS parametric distribution			
6	LogLogistic	Exponential	£166,292	£193,165
7		Weibull	£157,072	£169,530
8		Gamma	£164,485	£191,655
9		LogNormal	£157,377	£203,455
10		Gompertz	£152,215	£164,942
	Utilities			
11		Alternative health state utilities using the OHE value set for EQ-5D-5L valuation	£143,536	£200,778
12		Alternative health states utilities using one value (0.59) for all PD	£157,952	£219,640
	Dose / treatment duration			
13	Weibull	KM with Exponential tail for cobimetinib and vemurafenib (when in combination), TOT	£137,839	£209,942
14	LogLogistic	KM with LogNormal tail for vemurafenib (when monotherapy), TOT	£159,817	£209,942
15		PFS as a proxy for TOT for cobimetinib + vemurafenib vs. vemurafenib	£221,732	£209,942
16		Dosing as per label for cobimetinib + vemurafenib vs. vemurafenib	£170,305	£254,301
	Discount rate: effects and costs			
17	3.5%	1.5%	£140,198	£203,763
	Time horizon			
18	30	20	£152,911	£209,811
19		10	£169,632	£217,655
	Drug costs			
20		£0 cobimetinib	£53,358	£90,977

Summary of sensitivity analyses results

5.8.10 Describe the main findings of the sensitivity analyses, highlighting the key drivers of the cost-effectiveness results.

The sensitivity analysis highlighted that cobimetinib + vemurafenib is not cost-effective according to the standard threshold range employed by NICE.

Scenario analyses utilising different parametric functions for PFS and OS extrapolation, resulted in changes to the ICERs. ICERs mostly increased using alternative parametric functions for OS decreased for PFS. However these parameters were explored and deemed inappropriate due to both visual fit to the available data, and according to AIC criterion.

In the scenario where the cost of cobimetinib is set to zero, the additional cost of vemurafenib (through extension of PFS provided by the addition of cobimetinib) leads to an ICER which exceeds the standard cost-effectiveness thresholds: cost-effectiveness may only be demonstrated if the manufacturer provides an additional subsidy to the NHS. This scenario is clearly unsustainable for the manufacturer and not supportive of expanding patient access to innovative technologies

The limitations of standard HTA methodology when assessing combination treatments in metastatic disease are well recognised (Session IP19 ISPOR European congress 2015; Pertuzumab NICE Appraisal ID523), with a NICE Decision Support Unit (DSU) Technical Support Document (TSD) unable to offer a solution (Davis S 2014) Indeed, the appraisal of the first submission to encounter this issue – pertuzumab (in combination with trastuzumab) in metastatic breast cancer – is still on-going, despite evidence submissions being made in April 2013.

This perverse outcome of the methodology is ultimately to the detriment of groups of patients who remain in clear and recognised need of new therapies: the EMA's assessment of clinical effectiveness supports licensing, but reliance on cost-effectiveness analysis means that they cannot be approved for use in the NHS. The need for immediate collaboration between industry, NICE and the Department of Health to find a solution to this situation is now at a critical timepoint.

Patients with metastatic breast cancer who are eligible to receive pertuzumab have been able to do so through the Cancer Drugs Fund: this is not an option for patients with metastatic melanoma. Should an immediate solution to this methodological issue not be found, the Committee must take these circumstances into account when coming to a recommendation in this appraisal.

5.9 Subgroup analysis

5.9.1 – 5.9.6: Subgroup analysis

No subgroup analyses were performed.

5.10 Validation

Validation of de novo cost-effectiveness analysis

5.10.1 When describing the methods used to validate and quality assure the model, provide:

As discussed in sections 5.3.4, 5.4.13 and 5.5.4, Clinical and Health Economic experts were consulted to validate the appropriate methodological and clinical assumptions had been made. Also that model outputs were clinically plausible. Key aspects discussed included:

- The overall model structure and health states within the model
- Use of mix-model for OS extrapolation
- Methods for deriving utilities from EQ-5D-5L results from coBRIM
- Resource use included in the model

Experts agreed the model structure and health states were appropriate for the condition and appraisal scope. Use of the mix-model for OS extrapolation was deemed a robust approach both methodologically and clinically. Advise was given and followed on the use of the OHE value set for EQ-5D-5L (section 5.4.2), and resource use (section 5.5.4).

Internal quality control and validation of the model was conducted by York Health Economics Consortium (YHEC). Validation included a number of 'pressure tests', often using extreme values. The results of the model using these values were then compared to expected outputs to assess functionally accuracy.

5.11 Interpretation and conclusions of economic evidence

5.11.1 Are the results from this economic evaluation consistent with the published economic literature?

The literature search did not identify any existing cost-effectiveness studies assessing cobimetinib + vemurafenib in stage IIIb/IV melanoma.

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

The evaluation is in line with the licensed indication for cobimetinib + vemurafenib, and does not exclude any subgroups who are eligible to receive therapy.

- *How relevant (generalisable) is the analysis to clinical practice in England?*

When possible, England or UK specific data have been utilised for model inputs. The patients in the coBRIM study were considered generalisble to the English population, and this was validated with expert clinical advice.

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

For the OS extrapolation it was necessary to make various assumptions, which results in some uncertainty. However the approach taken to extrapolate OS is in line with previous ERG recommendations (Dickson 2012).

The main strengths of the evaluation are:

1. The model uses data from the pivotal clinical trial (coBRIM) wherever possible, and resource use and costs based on recent NICE technology appraisals.

2. coBRIM is a robust and well conducted study in people broadly representative of the population expected to be treated in England and Wales.

3. The model incorporates utilities taken directly from patients who have received cobimetinib + vemurafenib.

4. The incorporation of OS parameters into the model has been validated by external experts. The modelled results are clinically plausible and broadly match existing data sources where available.

    - *What further analyses could be carried out to enhance the robustness or completeness of the results?*

Limited long-term clinical data are available for cobimetinib + vemurafenib, thus the model heavily relies on extrapolation of clinical outcomes. Robustness of the model would be improved if more mature data were available.

6. Assessment of factors relevant to the NHS and other parties

6.1-6.2 How many people are eligible for treatment in England.

Patients eligible for treatment with cobimetinib + vemurafenib are those with BRAF V600 mutation-positive stage IIIb or IV melanoma. Table 61 presents the total eligible patients in England and the UK, should all eligible patients as per the licensed indication receive treatment.

Table 61 Patient algorithm for cobimetinib + vemurafenib eligible patients in UK (Roche 2016)

	Proportion	**Number**
Malignant melanoma	100%	11665
Stage IIIc / IV	22%	2524
BRAF V600 Mutated	34%	858
Systemic treatment	84%	721
Patients excluding clinical trials	88%	631
Total Eligible		**631**
	England	**551**
	Northern Ireland	17
	Scotland	38
	Wales	**25**

In line with the recent pembrolizumab (TA366, 2015) and nivolumab (ID845, 2016) NICE technology appraisals, an annual 3.5% increase in melanoma incidence is assumed to estimate eligible patients for Years 1 to 5 (2016 – 2020).

Table 62 English population eligible for treatment with cobimetinib + vemurafenib 2016 - 2020

	2016	**2017**	**2018**	**2019**	**2020**
BRAF V600 positive, stage IIIc/IV melanoma	551	570	590	611	632

6.3 *Explain any assumptions that were made about current treatment options and uptake of technologies.*

Assumptions regarding stage IIIb / IV melanoma patients (as seen in Table 61 above) include:

- All patients are BRAF mutation tested
- 34% are BRAF V600 mutation positive
- 22% of eligible patients enter clinical trials
- 3.5% annual incidence increase for malignant melanoma

6.4 *When relevant, explain any assumptions that were made about market share in England*.

Patients eligible for treatment with cobimetinib + vemurafenib have multiple treatment options available, including the recently appraised pembrolizumab. Given the dynamic nature of the market, accurate estimates of future market share are not possible. An assumption has been made that moving forward, 60% of patients with BRAF V600 mutation positive melanoma will receive targeted therapy. Subject to the ongoing appraisal of trametinib + dabrafenib (ID661), these patients will be eligible to receive either cobimetinib + vemurafenib, or trametinib + dabrafenib. In the absence of any available market share data, we assume a 50:50 split between these treatment options.

6.5 *Other significant costs associated with treatment*

Both cobimetinib and vemurafenib are oral medications, representing a low impact on administration resource use.

6.6 *Unit costs*

Unit costs are fully described in section 5.5 and are consistent with prior vemurafenib and dabrafenib NICE technology appraisals (TA269, 2012; TA321, 2014).

6.7 *If there were any estimates of resource savings, explain what they were and when they are likely to be made.*

Full breakdown of resource use for the intervention and comparators is presented in section 5.7.

6.8 *State the estimated annual budget impact on the NHS in England.*

The maximum number of patients eligible for treatment with cobimetinib + vemurafenib in England is 551 (Table 62). Applying the market share assumptions in 6.4 above, and assuming a 3.5% annual increase in incidence, budget impact of cobimetinib + vemurafenib is shown in Table 63 below. This table presents the total rather than incremental budget impact, therefore does not take into account the current spend on target therapy.

Table 63 Estimated budget impact in England over 5 years (List price)

	2016	**2017**	**2018**	**2019**	**2020**
Estimated total BRAF V600 mutant positive patients	551	570	590	611	632
Estimated share of market	165	171	177	183	190
Total costs	£151,578	£151,578	£151,578	£151,578	£151,578
Total treatment costs	£151,209	£151,209	£151,209	£151,209	£151,209
Total administration costs	£188	£188	£188	£188	£188
Total AE costs	£181	£181	£181	£181	£181
Total budget impact*	£25,010,370	£25,919,838	£26,829,306	£27,738,774	£28,799,820

*results presented for total, not incremental budget impact

6.9 *Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.*

No other resource saving or redirection is expected.

6.10 Highlight the main limitations within the budget impact analysis

The budget impact analysis is based on an assumption regarding future market share.

The average age of patients in the coBRIM study is 55 years old. This represents a population who are likely to be working; however this aspect of wider societal cost and benefit is not incorporated into the economic model or budget impact analysis.

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Cobimetinib draft Summary of Product Characteristics: 25th September 2015

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8. Appendices

Appendix 1: SmPC

1. Name of the medicinal product
Cotellic 20 mg film-coated tablets
2. Qualitative and quantitative composition
Each film-coated tablet contains cobimetinib hemifumarate equivalent to 20 mg cobimetinib.
Excipient with known effect:
Each film-coated tablet contains 36 mg lactose monohydrate.
For the full list of excipients, see section 6.1.
3. Pharmaceutical form
Film-coated tablet.
White, round film-coated tablets of approximately 6.6 mm diameter, with “COB” debossed on one side.
4. Clinical particulars
4.1 Therapeutic indications
Cotellic is indicated for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).
4.2 Posology and method of administration
Treatment with Cotellic in combination with vemurafenib should only be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.
Before starting this treatment, patients must have BRAF V600 mutation-positive melanoma tumour status confirmed by a validated test (see sections 4.4 and 5.1).
Posology
The recommended dose of Cotellic is 60 mg (3 tablets of 20 mg) once daily.
Cotellic is taken on a 28 day cycle. Each dose consists of three 20 mg tablets (60 mg) and should be taken once daily for 21 consecutive days (Days 1 to 21-treatment period); followed by a 7-day break (Days 22 to 28-treatment break). Each subsequent Cotellic treatment cycle should start after the 7-day treatment break has elapsed.
For information on the posology of vemurafenib, please refer to its SmPC.
Duration of treatment
Treatment with Cotellic should continue until the patient no longer derives benefit or until the development of unacceptable toxicity (see Table 1 below).
Missed doses
If a dose is missed, it can be taken up to 12 hours prior to the next dose to maintain the once-daily regimen.
Vomiting
In case of vomiting after administration of Cotellic, the patient should not take an additional dose on that day and treatment should be continued as prescribed the following day.
General dose modifications
The decision on whether to reduce the dose for either or both treatments should be based on the prescriber's assessment of individual patient safety or tolerability. Dose modification of Cotellic is independent of vemurafenib dose modification.
If doses are omitted for toxicity, these doses should not be replaced. Once the dose has been reduced, it should not be increased at a later time.
Table 1 below gives general Cotellic dose modification guidance.
Table 1 Recommended Cotellic dose modifications

Grade (CTC-AE)*	**Recommended Cotellic dose**
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain Cotellic at a dose of 60 mg once daily (3 tablets)
Grade 2 (intolerable) or Grade 3/4	
1st Appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 40 mg once daily (2 tablets)
2nd Appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 20 mg once daily (1 tablet)

3rd Appearance	Consider permanent discontinuation

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

Dose modification advice for left ventricular dysfunction

Permanent discontinuation of Cotellic treatment should be considered if cardiac symptoms are attributed to Cotellic and do not improve after temporary interruption.

Table 2 Recommended dose modifications for Cotellic in patients with left ventricular ejection fraction (LVEF) decrease from baseline

Patient	LVEF value	Recommended Cotellic dose modification	LVEF value following treatment break	Recommended Cotellic daily dose
Asymptomatic	≥ 50% (or 40-49% and < 10% absolute decrease from baseline)	Continue at current dose	N/A	N/A
	< 40% (or 40-49% and ≥ 10% absolute decrease from baseline)	Interrupt treatment for 2 weeks	< 10% absolute decrease from baseline	1st occurrence: 40 mg
				2nd occurrence: 20 mg
				3rd occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	N/A	Interrupt treatment for 4 weeks	Asymptomatic and < 10% absolute decrease from baseline	1st occurrence: 40 mg
				2nd occurrence: 20 mg
				3rd occurrence: permanent discontinuation
			Asymptomatic and < 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
			Symptomatic regardless of LVEF	Permanent discontinuation

N/A = Not Applicable

Vemurafenib treatment can be continued when Cotellic treatment is modified, if clinically indicated.

Dose modification advice for Cotellic when used with vemurafenib

Liver laboratory abnormalities

For Grade 1 and 2 liver laboratory abnormalities, Cotellic and vemurafenib should be continued at the prescribed dose.

Grade 3: Cotellic should be continued at the prescribed dose. The dose of vemurafenib may be reduced as clinically appropriate. Please refer to the vemurafenib SmPC.

Grade 4:

Cotellic treatment and vemurafenib treatment should be interrupted. If liver laboratory abnormalities improve to Grade ≤1 within 4 weeks, Cotellic should be restarted at a dose reduced by 20 mg and vemurafenib at a clinically appropriate dose, per its SmPC.

Cotellic treatment and vemurafenib treatment should be discontinued if liver laboratory abnormalities do not resolve to Grade ≤1 within 4 weeks or if Grade 4 liver laboratory abnormalities recur after initial improvement.

Creatine phosphokinase (CPK) elevations

Cotellic dosing does not need to be modified or interrupted to manage asymptomatic CPK elevations.

Photosensitivity

Grade ≤2 (tolerable) photosensitivity should be managed with supportive care.

Grade 2 (intolerable) or Grade ≥3 photosensitivity: Cotellic and vemurafenib should be interrupted until resolution to Grade ≤1. Treatment can be restarted with no change in Cotellic dose. Vemurafenib dosing should be reduced as clinically appropriate, please refer to its SmPC for further information.
Rash
Rash events may occur with either Cotellic or vemurafenib treatment. The dose of Cotellic and/or vemurafenib may be either temporarily interrupted and/or reduced as clinically indicated.
Additionally, for:
Grade ≤2 (tolerable) rash should be managed with supportive care. Cotellic dosing can be continued without modification.
Grade 2 (intolerable) or Grade ≥3 acneiform rash: General dose modification recommendations in Table 1 for Cotellic should be followed. Vemurafenib dosing can be continued when Cotellic treatment is modified (if clinically indicated).
Grade 2 (intolerable) or Grade ≥3 non-acneiform or maculopapular rash: Cotellic dosing can be continued without modification if clinically indicated. Vemurafenib dosing may be either temporarily interrupted and/or reduced, please refer to its SmPC for further information.
QT prolongation
If during treatment the QTc exceeds 500 msec, please refer to the vemurafenib SmPC (section 4.2) for dose modifications for vemurafenib. No dose modification of Cotellic is required when taken in combination with vemurafenib.
Special populations
Elderly patients
No dose adjustment is required in patients aged ≥65 years old.
Renal impairment
No dose adjustment is recommended in patients with mild or moderate renal impairment based on population pharmacokinetic analysis (see section 5.2). There are minimal data for Cotellic in patients with severe renal impairment, therefore an effect cannot be excluded. Cotellic should be used with caution in patients with severe renal impairment.
Hepatic impairment
The safety and efficacy of Cotellic has not been established in patients with hepatic impairment (see section 5.2). There are no pharmacokinetic data in patients with moderate or severe hepatic impairment. Cotellic should be used with caution in patients with moderate to severe hepatic impairment.
Non-Caucasian patients
The safety and efficacy of Cotellic in non-Caucasian patients have not been established.
Paediatric population
The safety and efficacy of Cotellic in children and adolescents below 18 years of age have not been established. No data are available.
Method of administration
Cotellic is for oral use. The tablets should be swallowed whole with water. They can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Before taking Cotellic in combination with vemurafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test.
Cotellic in combination with vemurafenib in patients who have progressed on a BRAF inhibitor
There are limited data in patients taking the combination of Cotellic with vemurafenib who have progressed on a prior BRAF inhibitor. These data show that the efficacy of the combination will be lower in these patients (see section 5.1). Therefore other treatment options should be considered before treatment with the combination in this prior BRAF inhibitor treated population. The sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.
Cotellic in combination with vemurafenib in patients with brain metastases
The safety and efficacy of the combination of Cotellic and vemurafenib have not been evaluated in patients with a BRAF V600 mutation-positive melanoma which has metastasised to the brain. The intracranial activity of cobimetinib is currently unknown (see sections 5.1 and 5.2).
Serous retinopathy
Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK-inhibitors, including Cotellic (see section 4.8). The majority of events were reported as chorioretinopathy or retinal detachment.

Median time to initial onset of serous retinopathy events was 1 month (range 0-9 months). Most events observed in clinical trials were resolved, or improved to asymptomatic Grade 1, following dose interruption or reduction.
Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances are identified, an ophthalmologic examination is recommended. If serous retinopathy is diagnosed, Cotellic treatment should be withheld until visual symptoms improve to Grade ≤1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Table 1 in section 4.2).
Left ventricular dysfunction
Decrease in LVEF from baseline has been reported in patients receiving Cotellic (see section 4.8). Median time to initial onset of events was 4 months (1-7 months).
LVEF should be evaluated before initiation of treatment to establish baseline values, then after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation (see section 4.2).
All patients restarting treatment with a dose reduction of Cotellic should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated. Patients with a baseline LVEF either below institutional lower limit of normal (LLN) or below 50% have not been studied.
Liver laboratory abnormalities
Liver laboratory abnormalities can occur when Cotellic is used in combination with vemurafenib and with vemurafenib as a single agent (please refer to its SmPC).
Liver laboratory abnormalities, specifically increases in Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Alkaline Phosphatase (ALP), have been observed in patients treated with Cotellic plus vemurafenib (see section 4.8).
Liver value abnormalities should be monitored by liver laboratory tests before initiation of combination treatment and monthly during treatment, or more frequently as clinically indicated (see section 4.2). Grade 3 liver laboratory abnormalities should be managed with vemurafenib treatment interruption or dose reduction. Manage Grade 4 liver laboratory abnormalities with treatment interruption, dose reduction or with treatment discontinuation of both Cotellic and vemurafenib (see section 4.2).
Diarrhoea
Cases of Grade ≥3 and serious diarrhoea have been reported in patients treated with Cotellic. Diarrhoea should be managed with anti-diarrhoeal agents and supportive care. For Grade ≥3 diarrhoea that occurs despite supportive care, Cotellic and vemurafenib should be withheld until diarrhoea has improved to Grade ≤1. If Grade ≥3 diarrhoea recurs, the dose of Cotellic and vemurafenib should be reduced (see section 4.2).
Lactose intolerance
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, congenital lactase deficiency or glucose-galactose malabsorption should consult with their physician and discuss whether the benefits outweigh the risks on an individual basis.
Drug-drug interactions: CYP3A4 inhibitors
Concurrent use of strong CYP3A inhibitors during treatment with Cotellic should be avoided. Caution should be exercised if a moderate CYP3A4 inhibitor is co-administered with Cotellic. If concomitant use with a strong or moderate CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety and dose modifications applied if clinically indicated (see Table 1 in section 4.2).
QT prolongation
If during treatment the QTc exceeds 500 msec, please refer to the vemurafenib SmPC sections 4.2 and 4.4.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on cobimetinib
CYP3A inhibitors
Cobimetinib is metabolized by CYP3A and cobimetinib AUC increased approximately 7 fold in the presence of a strong CYP3A inhibitor (itraconazole) in healthy subjects. The magnitude of interaction could potentially be lower in patients.
Strong CYP3A4 inhibitors (see section 4.4.): Avoid concurrent use of strong CYP3A inhibitors during treatment with cobimetinib. Strong CYP3A4 inhibitors include, but are not limited to ritonavir, cobicistat, telaprevir, lopinavir, itraconazole, voriconazole, clarithromycin, telithromycin, posaconazole, nefazodone and grapefruit juice. If concomitant use of a strong CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety. For strong CYP3A inhibitors used short-term (7 days or less), consider interrupting cobimetinib therapy during the duration of inhibitor use.

Moderate CYP3A4 inhibitors (see section 4.4.): Caution should be exercised if cobimetinib is co-administered with moderate CYP3A inhibitors. Moderate CYP3A4 inhibitors include, but are not limited to, amiodarone, erythromycin, fluconazole, miconazole, diltiazem, verapamil, delavirdine, amprenavir, fosamprenavir, imatinib. When cobimetinib is co-administered with a moderate CYP3A inhibitor, patients should be carefully monitored for safety.
Mild CYP3A4 inhibitors: Cobimetinib can be co-administered with mild inhibitors of CYP3A without dose adjustment.
CYP3A inducers
Co-administration of cobimetinib with a strong CYP3A inducer was not assessed in a clinical study, however, a reduction in cobimetinib exposure is likely. Therefore, concomitant use of moderate and strong CYP3A inducers (e.g. carbamazepine, rifampicin, phenytoin, and St. John's Wort) should be avoided. Alternative agents with no or minimal CYP3A induction should be considered. Given that cobimetinib concentrations are likely to be significantly reduced when co-administered with moderate to strong CYP3A inducers, patient's efficacy may be compromised.
P-glycoprotein inhibitors
Cobimetinib is a substrate of P-glycoprotein (P-gp). Concomitant administration of P-gp inhibitors such as ciclosporin and verapamil may have the potential to increase plasma concentrations of cobimetinib.
Effects of cobimetinib on other medicinal products
CYP3A and CYP2D6 substrates
A clinical drug-drug interaction (DDI) study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A substrate) and dextromethorphan (a sensitive CYP2D6 substrate) were not altered in the presence of cobimetinib.
CYP1A2 substrates
In vitro, cobimetinib is a potential inducer of CYP1A2 and may therefore reduce the exposure of substrates of this enzyme*e.g.,* theophylline. No clinical DDI studies have been conducted to assess the clinical relevance of this finding.
BCRP substrates
In vitro, cobimetinib is a moderate inhibitor of BCRP (Breast Cancer Resistance Protein). No clinical DDI studies have been conducted to assess this finding, and clinically relevant inhibition of intestinal BCRP cannot be ruled out.
Other anti-cancer agents
Vemurafenib
There is no evidence of any clinically significant drug-drug interaction between cobimetinib and vemurafenib in unresectable or metastatic melanoma patients and therefore no dose adjustments is recommended.
Effects of cobimetinib on drug transport systems
In vitro studies show that cobimetinib is not a substrate of the liver uptake transporters OATP1B1, OATP1B3 and OCT1, however, it weakly inhibits these transporters. The clinical relevance of these findings has not been investigated.
Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should be advised to use two effective contraceptive methods, such as a condom or other barrier method (with spermicide, if available) during treatment with Cotellic and for at least three months following treatment discontinuation.
Pregnancy
There are no data from the use of Cotellic in pregnant women. Studies in animals have shown embryolethality and foetal malformations of the great vessels and skull (see section 5.3). Cotellic should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.
Breast-feeding
It is not known whether cobimetinib is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or discontinue Cotellic therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Fertility

There are no data in humans for cobimetinib. In animals, no fertility studies have been performed, but adverse effects were seen on female reproductive organs (see section 5.3). The clinical relevance of this is unknown.

4.7 Effects on ability to drive and use machines

Cotellic has minor influence on the ability to drive or use machines. Visual disturbances have been reported in some patients treated with cobimetinib during clinical trials (see sections 4.4 and 4.8). Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse effects that may affect their ability.

4.8 Undesirable effects

Summary of the safety profile

The safety of Cotellic in combination with vemurafenib has been evaluated in 254 patients with advanced BRAF V600 mutated melanoma in Study GO28141.The median time to onset of first Grade ≥3 adverse events was 0.5 months in the Cotellic plus vemurafenib arm vs 0.8 months in the placebo plus vemurafenib arm.

The safety of Cotellic in combination with vemurafenib has also been evaluated in 129 patients with advanced BRAF V600 mutated melanoma in Study NO25395. The safety profile of Study NO25395 was consistent with that observed in Study GO28141.

In Study GO28141, the most common adverse reactions (>20%) observed with a higher frequency in the Cotellic plus vemurafenib arm were diarrhoea, rash, nausea, pyrexia, photosensitivity reaction, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood creatine phosphokinase, and vomiting. The most common adverse reactions (>20%) observed with a higher frequency in the placebo plus vemurafenib arm were arthralgia, alopecia, and hyperkeratosis. Fatigue was observed at similar frequencies in both arms.

Please refer to the vemurafenib SmPC for complete descriptions of all undesirable effects associated with vemurafenib treatment.

Tabulated list of adverse reactions

ADRs are based on results from a multi-centre, randomised, double-blind, placebo-controlled, Phase III Study (GO28141) that evaluated the safety and efficacy of Cotellic in combination with vemurafenib as compared to vemurafenib alone in previously untreated BRAF V600 mutation-positive patients with unresectable locally advanced (Stage IIIc) or metastatic melanoma (Stage IV).

ADRs which were reported in melanoma patients are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been used for the classification of frequency:

Very common ≥ 1/10
Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1,000 to < 1/100
Rare ≥ 1/10,000 to < 1/1,000
Very rare < 1/10,000

Table 3 lists adverse reactions considered associated with the use of Cotellic. Within each frequency grouping, ADRs are presented in order of decreasing severity and were reported according to NCI-CTCAE v 4.0 (common toxicity criteria) for assessment of toxicity in Study GO28141.

Table 3 Adverse drug reactions in patients treated with Cotellic in combination with vemurafenib in Study GO28141

System organ class	Very Common	Common
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		Basal cell carcinoma, Cutaneous squamous cell carcinoma**, Keratoacanthoma**
Blood and lymphatic system disorders	Anaemia	
Metabolism and nutrition disorders		Dehydration, Hypophosphataemia, Hyponatremia, Hyperglycaemia
Eye disorders	Serous retinopathy[a]	Blurred vision, Visual impairment
Vascular disorders	Hypertension, Haemorrhage*	
Respiratory, thoracic and mediastinal disorders		Pneumonitis
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting	
Skin and subcutaneous tissue	Photosensitivity[b], Rash, Rash	

disorders	maculo-papular, Dermatitis acneiform, Hyperkeratosis**	
General disorders and administration site conditions	Pyrexia	Chills
Investigations	Blood CPK increased, ALT increased, AST increased, Gamma-Glutamyltransferase (GGT) increased, Blood ALP increased	Ejection fraction decreased, Blood bilirubin increased

* Please refer to the paragraph *Haemorrhage* in the"Description of selected adverse reactions" section

** Please refer to the paragraph C*utaneous squamous cell carcinoma, keratoacanthoma and hyperkeratosis* in the “Description of selected adverse reactions” section.

[a] Includes both chorioretinopathy and retinal detachment events indicative of serous retinopathy (see section 4.4)

[b] Combined figure includes reports of photosensitivity reaction, sunburn, solar dermatitis, actinic elastosis

Description of selected adverse reactions

Haemorrhage

Bleeding events have been reported more frequently in the Cotellic plus vemurafenib arm than in the placebo plus vemurafenib arm (all types and Grades: 10% vs 6%). Higher frequencies in the Cotellic plus vemurafenib arm were observed for cerebral haemorrhage (1% vs 0%), gastrointestinal tract haemorrhage (3% vs 1%), reproductive system haemorrhage (2% vs 1%) and haematuria (2% vs 1%).

The majority of events were Grade 1 or 2 and non-serious (9% of patients in the Cotellic plus vemurafenib arm vs 5% patients in the placebo plus vemurafenib arm). Grade 3-5 events were experienced by 1% and 0.4% of patients, respectively. The median time to first onset was 2.8 months (range 0.0 to 12.7 months) in the Cotellic plus vemurafenib arm.

Photosensitivity

Photosensitivity has been observed with a higher frequency in the Cotellic plus vemurafenib arm vs placebo plus vemurafenib arm (41% vs 31%). The majority of events were Grades 1 or 2, with Grade ≥3 events occurring in 3% of patients in the Cotellic plus vemurafenib arm vs 0% in the placebo plus vemurafenib arm.

There were no apparent trends in the time of onset of Grade ≥3 events. Grade ≥3 photosensitivity events in the Cotellic plus vemurafenib arm were treated with primary topical medicinal products in conjunction with dose interruptions of both cobimetinib and vemurafenib (see section 4.2).

No evidence of phototoxicity was observed with Cotellic as a single agent.

Cutaneous squamous cell carcinoma, keratoacanthoma and hyperkeratosis

Cutaneous squamous cell carcinoma has been reported with a lower frequency in the Cotellic plus vemurafenib arm vs placebo plus vemurafenib arm (all Grade: 3% vs 11%). Keratoacanthoma has been reported with a lower frequency in the Cotellic plus vemurafenib arm vs placebo plus vemurafenib arm (all Grade: 1% vs 8%). Hyperkeratosis has been reported with a lower frequency in the Cotellic plus vemurafenib vs placebo plus vemurafenib arm (all Grade: 10% vs 29%).

Serous retinopathy

Cases of serous retinopathy have been reported in patients treated with Cotellic (see section 4.4.) For patients reporting new or worsening visual disturbances, an ophthalmologic examination is recommended. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Table 1 in section 4.2).

Left ventricular dysfunction

Decrease in LVEF from baseline has been reported in patients receiving Cotellic (see section 4.4). LVEF should be evaluated before initiation of treatment to establish baseline values, then after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation (see section 4.2).

Laboratory abnormalities

Liver laboratory abnormalities

Liver laboratory abnormalities, specifically ALT, AST, and ALP have been observed in patients treated with Cotellic in combination with vemurafenib (see section 4.4).

Liver laboratory tests should be monitored before initiation of combination treatment and monthly during treatment, or more frequently if clinically indicated (see section 4.2).

Blood creatine phosphokinase increase

Asymptomatic increases in blood CPK levels were observed with a higher frequency in the Cotellic plus vemurafenib arm vs placebo plus vemurafenib arm in Study GO28141 (see section 4.2). One event of rhabdomyolysis was observed in each treatment arm of the Study with concurrent increases in blood CPK.

Table 4 provides the frequency of measured liver laboratory abnormalities and elevated creatine phosphokinase for all Grades and Grades 3-4.

Table 4 Liver and other laboratory tests observed in the Phase III Study GO28141

Changes in reported laboratory data	**Cobimetinib plus Vemurafenib (n = 254) (%)**		**Placebo plus Vemurafenib (n = 239) (%)**	
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**
Liver function test				
Increased ALP	69	7	54	3
Increased ALT	66	10	53	6
Increased AST	69	7	42	2
Increased GGT	60	19	59	17
Increased blood bilirubin	33	2	43	1
Other laboratory abnormalities				
Increased blood CPK	65	11	13	<1

Special populations

Elderly patients

In the Phase III study with Cotellic in combination with vemurafenib in patients with unresectable or metastatic melanoma (n=254), 189 patients (74%) were <65 years of age, and 44 patients (17%) were 65-74 years of age, 17 (7%) were 75-84 years of age, and 4 patients (2%) were aged ≥85 years The proportion of patients experiencing adverse events (AE) was similar in the patients aged <65 years and those aged ≥65 years. Patients ≥65 years were more likely to experience serious adverse events (SAEs) and experience AEs leading to discontinuation of cobimetinib than those <65 years.

Renal impairment

No pharmacokinetic trial in subjects with renal impairment has been conducted. Dose adjustment is not recommended for mild to moderate renal impairment based on the results of the population pharmacokinetic analysis. There are minimal data for Cotellic in patients with severe renal impairment. Cotellic should be used with caution in patients with severe renal impairment.

Hepatic impairment

No pharmacokinetic data in subjects with hepatic impairment are available.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions (see details below).

Ireland

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

Malta

ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

United Kingdom

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

There is no experience with overdose in human clinical trials. In case of suspected overdose, cobimetinib should be withheld and supportive care instituted. There is no specific antidote for overdosage with cobimetinib.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, ATC code: L01XE38

Mechanism of action

Cobimetinib is a reversible, selective, allosteric, oral inhibitor that blocks the mitogen-activated protein kinase (MAPK) pathway by targeting the mitogen-activated extracellular signal-regulated kinase (MEK) 1 and MEK 2 which results in inhibition of phosphorylation of the extracellular signal-regulated kinase (ERK) 1 and ERK 2. Therefore, cobimetinib blocks the cell proliferation induced by the MAPK pathway through inhibition of the MEK1/2 signalling node.

In the preclinical models, the combination of cobimetinib and vemurafenib showed that by simultaneously targeting mutated BRAF V600 proteins and MEK proteins in melanoma cells, the combination of the two products inhibits MAPK pathway reactivation through MEK1/2, resulting in a stronger inhibition of intracellular signalling and decreased tumour cell proliferation

Clinical efficacy and safety

There are no data on the safety or efficacy of Cotellic in combination with vemurafenib in patients with central nervous system metastasis or in patients with non-cutaneous malignant melanoma.

Study GO28141 (coBRIM)

Study GO28141 is a multi-centre, randomised, double-blind, placebo-controlled, Phase III study to evaluate the safety and efficacy of Cotellic in combination with vemurafenib as compared to vemurafenib plus placebo, in previously untreated patients with BRAF V600 mutation-positive unresectable locally advanced (Stage IIIc) or metastatic melanoma (Stage IV).

Only patients with ECOG performance status 0 and 1 were enrolled in Study GO28141. Patients with ECOG performance status 2 or higher were excluded from the study.

Following confirmation of a BRAF V600 mutation, using the cobas® 4800 BRAF V600 mutation test, 495 previously untreated patients with unresectable locally advanced or metastatic melanoma were randomised to receive either:

• Placebo once daily on Days 1-21 of each 28-day treatment cycle and 960 mg vemurafenib twice daily on Days 1-28, or

• Cotellic 60 mg once daily on Days 1-21 of each 28-day treatment cycle and 960 mg vemurafenib twice daily on Days 1-28

Progression-free survival (PFS) as assessed by the investigator (INV) was the primary endpoint. Secondary efficacy endpoints included overall survival (OS), objective response rate, duration of response (DoR) as assessed by INV and PFS as assessed by an independent review facility (IRF).

Key baseline characteristics included: 58% of patients were male, median age was 55 years (range 23 to 88 years), 60% had metastatic melanoma stage M1c and the proportion of patients with elevated LDH was 46.3% in the cobimetinib plus vemurafenib arm and 43.0% in the placebo plus vemurafenib arm.

In Study GO28141, there were 89 patients (18.1%) aged 65-74, 38 patients (7.7%) aged 75-84 and 5 patients (1.0%) aged 85 years and older.

Efficacy results are summarized in Table 5.

Table 5 Efficacy results from Study GO28141 (coBRIM) – Cut-off date 16 January 2015

	Cotellic + vemurafenib N=247	**Placebo + vemurafenib N=248**
Primary Endpoint[a]		
Progression-Free Survival (PFS)		
Median (months) 95 % CI	12.3 (9.5, 13.4)	7.2 (5.6, 7.5)
Hazard ratio (95% CI) [b]	0.58 (0.46; 0.72)	
Key Secondary Endpoints[a]		
Overall Survival (OS)		
OS % at 12 months (95% CI)	74.9 (69.3, 80.5)	63.0 (56.8, 69.3)
Median (months) 95 % CI	NE (20.7, NE)	17.0 (15.0, NE)

Hazard ratio (95% CI)[b]	0.65 (0.49, 0.87)	
Objective response rate (ORR)	172 (69.6%)	124 (50.0%)
95% CI for ORR[c]	(63.5%, 75.3%)	(43.6%, 56.4%)
Difference in ORR % (95% CI) [d]	19.6 (11.0, 28.3)	
Best Overall Response		
Complete Response	39 (15.8%)	26 (10.5%)
Partial Response	133 (53.8%)	98 (39.5%)
Stable disease	44 (17.8%)	92 (37.1%)
Duration of Response (DoR)		
Median DoR (months) 95% CI for median	13 (11.1, 16.6)	9.2 (7.5, 12.8)

NE = Not evaluable

[a] Assessed and confirmed by the investigator (INV) using RECIST v1.1

[b] Stratified analysis by geographic region and metastasis classification (disease stage)

[c] Using Clopper-Pearson method

[d] Using Hauck-Anderson method

The primary analysis for Study GO28141 was conducted with a data cut-off date of 09 May 2014. Significant improvement in the primary endpoint, investigator-assessed PFS, was observed in patients assigned to the Cotellic plus vemurafenib arm compared to the placebo plus vemurafenib arm (HR 0.51 (0.39; 0.68); p-value < 0.0001). The median estimate for investigator-assessed PFS was 9.9 months for the Cotellic plus vemurafenib arm vs. 6.2 months for the placebo plus vemurafenib arm. The median estimate for independent review of PFS was 11.3 months for the Cotellic plus vemurafenib arm vs. 6.0 months for the placebo plus vemurafenib arm (HR 0.60 (0.45; 0.79); p-value = 0.0003). The objective response rate (ORR) in the Cotellic plus vemurafenib arm was 67.6% vs 44.8% in the placebo plus vemurafenib arm. The difference in ORR was 22.9 % (p-value<0.0001).

Figure 1 Kaplan-Meier curves of progression-free survival (INV) – intent to treat population (cut-off date: 16 January 2015)

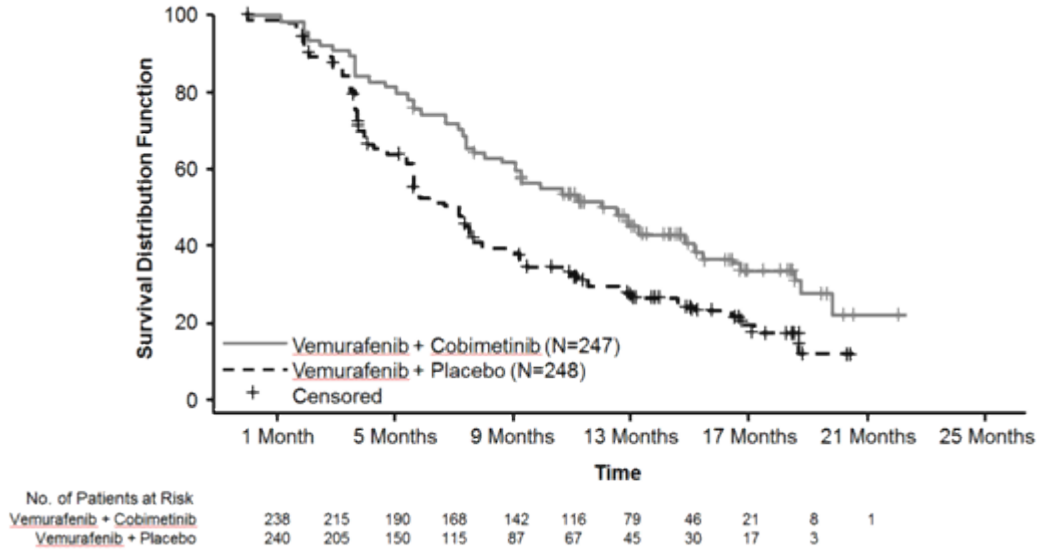
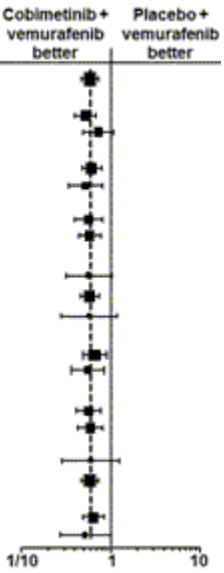


Figure 2 Forest plot for hazard ratios of progression-free survival subgroup analyses – intent to treat population (cut-off date: 16 January 2015)

Baseline Risk Factors	Total n	Placebo + vemurafenib (n=248) n	Events	Median (months)	Cobimetinib + vemurafenib (n=247) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	495	248	180	7.2	247	143	12.3	0.59	(0.47, 0.73)
Disease Stage (IIIc/M1a/M1b, or M1c)									
M1c	299	153	128	5.5	146	94	9.5	0.52	(0.40, 0.68)
Unresectable Stage IIIc/M1a/M1b	196	95	52	11.0	101	49	13.4	0.73	(0.49, 1.08)
Age Group (yr)									
< 65	362	179	128	7.2	183	107	12.6	0.61	(0.47, 0.79)
≥ 65	133	69	52	5.6	64	36	11.2	0.52	(0.34, 0.80)
Sex									
Female	209	108	72	7.5	101	52	12.9	0.57	(0.40, 0.82)
Male	286	140	108	5.7	146	91	11.1	0.58	(0.44, 0.77)
Geographic Region									
Australia/New Zealand/Others	78	38	26	7.4	40	20	13.3	0.57	(0.32, 1.03)
Europe	366	184	138	6.0	182	107	11.2	0.58	(0.45, 0.75)
N. America	51	26	16	7.5	25	16	11.2	0.57	(0.28, 1.17)
ECOG Performance Status									
0	348	164	110	7.6	184	100	12.9	0.65	(0.49, 0.85)
1	138	80	66	5.5	58	41	10.0	0.53	(0.35, 0.78)
Screening Serum LDH									
Elevated	216	104	85	5.4	112	78	8.2	0.57	(0.42, 0.78)
Normal	268	138	90	7.8	130	65	13.4	0.59	(0.43, 0.81)
Prior Adjuvant Therapy									
Yes	48	24	16	7.2	24	12	16.5	0.60	(0.28, 1.27)
No	447	224	164	7.2	223	131	11.2	0.59	(0.47, 0.74)
BRAF^{V600} Mutation Status									
V600E	344	174	126	7.2	170	102	10.6	0.64	(0.49, 0.83)
V600K	56	32	24	6.0	24	14	12.4	0.52	(0.27, 1.02)



Global health status / health-related quality of life by patient-report were measured using the EORTC Quality of Life Questionnaire – Core 30 (QLQ-C30). All functioning domains and most symptoms (appetite loss, constipation, insomnia, nausea and vomiting, dyspnoea, pain, fatigue) were similar between the two treatment arms and did not demonstrate a clinically meaningful change (≥ 10 point increase or decrease from baseline).

Study NO25395 (BRIM7)

The efficacy of Cotellic was evaluated in Phase Ib Study, NO25395, which was designed to assess the safety, tolerability, pharmacokinetics and efficacy of Cotellic when added to vemurafenib for the treatment of patients with BRAFV600 mutation-positive (as detected by the cobas® 4800 BRAF V600 Mutation Test), unresectable or metastatic melanoma.

This study treated 129 patients with Cotellic and vemurafenib: 63 were BRAF inhibitor (BRAFi) therapy naïve and 66 patients had previously progressed on prior vemurafenib therapy. Among the 63 BRAFi naïve patients, 20 patients had received prior systemic therapy for advanced melanoma with the majority (80%) being immunotherapy.

Results of the BRAFi naïve population from Study NO25395 were generally consistent with those from Study GO28141. The BRAFi-naïve patients (n=63) attained an 87% objective response rate, including a complete response in 10% of patients. The median duration of response was 12.5 months. The median PFS for BRAFi-naïve patients was 13.7 months, with median follow-up time of 12.7 months.

Among patients who had progressed on vemurafenib (n=66), the objective response rate was 15%. The median duration of response was 6.7 months. The median PFS for patients who had progressed on vemurafenib was 2.8 months.

In patients who were naive to BRAF inhibitor therapy, the overall survival at 1-year was 83% (95% CI 73, 93). In patients who had progressed on BRAF inhibitor therapy, the overall survival at 1-year was 32% (95% CI 19, 45).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Cotellic in one or more subsets of the paediatric population in malignant solid tumours (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral dosing of 60 mg in cancer patients, cobimetinib showed a moderate rate of absorption with a median T_{max} of 2.4 hours. The mean steady-state C_{max} and AUC_{0-24} were 273 ng/mL and 4340 ng.h/mL respectively. The mean accumulation ratio at steady state was approximately 2.4-fold. Cobimetinib has linear pharmacokinetics in the dose range of ~3.5 mg to 100 mg.

The absolute bioavailability of cobimetinib was 45.9% (90% CI: 39.7%, 53.1%) in healthy subjects. A human mass balance study was conducted in healthy subjects, and showed that cobimetinib was extensively metabolised and eliminated in faeces. The fraction absorbed was ~88% indicating high absorption and first pass metabolism.

The pharmacokinetics of cobimetinib are not altered when administered in the fed state (high-fat meal) compared with the fasted state in healthy subjects. Since food does not alter the pharmacokinetics of cobimetinib, it can be administered with or without food.

Distribution

Cobimetinib is 94.8% bound to human plasma proteins *in vitro*. No preferential binding to human red blood cells was observed (blood to plasma ratio 0.93).

The volume of distribution was 1050 L in healthy subjects given an intravenous dose of 2 mg. The apparent volume of distribution was 806 L in cancer patients based on population pharmacokinetic analysis.

Cobimetinib is a substrate of P-gp *in vitro*. The transport across the blood brain barrier is unknown.

Biotransformation

Oxidation by CYP3A and glucuronidation by UGT2B7 appear to be the major pathways of cobimetinib metabolism. Cobimetinib is the predominant moiety in plasma. No oxidative metabolites greater than 10% of total circulating radioactivity or human specific metabolites were observed in plasma. Unchanged medicinal product in faeces and urine accounted for 6.6% and 1.6% of the administered dose, respectively, indicating that cobimetinib is primarily metabolised with minimal renal elimination. *In vitro* data indicate cobimetinib is not an inhibitor of OAT1, OAT3 or OCT2.

Elimination

Cobimetinib and its metabolites were characterised in a mass balance study in healthy subjects. On average, 94% of the dose was recovered within 17 days. Cobimetinib was extensively metabolised and eliminated in faeces.

Following intravenous administration of a 2 mg dose of cobimetinib, the mean plasma clearance (CL) was 10.7 L/hr. The mean apparent CL following oral dosing of 60 mg in cancer patients was 13.8 L/hr. The mean elimination half-life following oral dosing of cobimetinib was 43.6 hours (range: 23.1 to 69.6 hours). Therefore, it may take up to 2 weeks following treatment cessation for cobimetinib to be completely removed from systemic circulation.

Special populations

Based on a population pharmacokinetic analysis, gender, race, ethnicity, baseline ECOG, mild and moderate renal impairment did not affect the pharmacokinetic of cobimetinib. Baseline age and baseline body weight were identified as statistically significant covariates on cobimetinib clearance and volume of distribution respectively. However, sensitivity analysis suggests neither of these covariates had clinically significant impact on steady state exposure.

Gender

Gender does not have an effect on the exposure of cobimetinib, based on a population pharmacokinetic analysis including 210 women and 277 men.

Elderly

Age does not have an effect on the exposure of cobimetinib, based on a population pharmacokinetic analysis including 133 patients ≥ 65 years of age.

Renal impairment

Based on preclinical data and the human mass balance study, cobimetinib is mainly metabolised, with minimal renal elimination. No formal pharmacokinetic study has been conducted in patients with renal impairment.

A population pharmacokinetic analysis using data from 151 patients with mild renal impairment (creatinine clearance (CRCL) 60 to less than 90 mL/min), 48 patients with moderate renal impairment (CRCL 30 to less than 60 mL/min), and 286 patients with normal renal function (CRCL greater than or equal to 90 mL/min), showed that CRCL had no meaningful influence on exposure of cobimetinib. Mild to moderate renal impairment does not influence cobimetinib exposure based on the population pharmacokinetic analysis. There are minimal data for Cotellic in patients with severe renal impairment.

Hepatic impairment

No pharmacokinetic data in subjects with hepatic impairment are available.

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of cobimetinib in paediatric patients.

5.3 Preclinical safety data

Carcinogenicity studies have not been conducted with cobimetinib. Standard genotoxicity studies with cobimetinib were negative.

No dedicated fertility studies in animals have been performed with cobimetinib. In the repeat-dose toxicology studies, degenerative changes were observed in reproductive tissues including increased

apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal epithelial cells in rats, and epididymal epithelial cells in dogs. The clinical relevance of this is unknown.
When administered to pregnant rats, cobimetinib caused embryolethality and foetal malformations of the great vessels and skull at systemic exposures similar to human exposure at recommended dose.
Cardiovascular safety of cobimetinib in combination with vemurafenib has not been evaluated *in vivo*. *In vitro*, cobimetinib produced moderate hERG ion channel inhibition (IC_{50}= 0.5 µM [266 ng/mL]), which is approximately 18 fold higher than peak plasma concentrations (C_{max}) at the 60 mg to be marketed dose (unbound C_{max}=14 ng/mL [0.03 µM]).
Toxicity studies in rats and dogs identified generally reversible degenerative changes in the bone marrow, gastrointestinal tract, skin, thymus, adrenal gland, liver, spleen, lymph node, kidney, heart, ovary, and vagina at plasma exposures below clinical efficacious levels. Dose limiting toxicities included skin ulcerations, surface exudates, and acanthosis in the rat and chronic active inflammation and degeneration of the oesophagus associated with varying degrees of gastroenteropathy in dogs.
In a repeat dose toxicity study in juvenile rats, cobimetinib systemic exposures were 2 to11 fold higher on post natal day 10 than on post natal day 38 when exposures were similar to those in adult rats. In juvenile rats, cobimetinib administration resulted in similar changes as seen in the pivotal toxicity studies in adults, including reversible degenerative changes in the thymus and liver, decreased spleen and thyroid/parathyroid weights, increased phosphorus, bilirubin and red blood cell mass and decreased triglycerides. Mortality occurred in juvenile animals at a dose (3 mg/kg) which did not lead to mortalities in adult animals.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)
Film coating
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC/PVDC blisters containing 21 tablets. Each pack contains 63 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. Marketing authorisation number(s)

EU/1/15/1048/001

9. Date of first authorisation/renewal of the authorisation

20 November 2015

10. Date of revision of the text

15 December 2015
Detailed information on this medicinal product is available on the website of the European Medicines Agencyhttp://www.ema.europa.eu.

Appendix 2: Search strategy for relevant studies

The search terms for each database searched can be found in the following tables.

No limits were applied to any of the searches.

- Table 64: MEDLINE, MEDLINE In-Process and Embase via Ovid SP
- Table 65: Embase Alert via ProQuest
- Table 66: Cochrane Library Databases via the Wiley Online platform
- Table 67: Congress proceedings

- **Table 64. Search terms for the RCT search of MEDLINE, MEDLINE In-Process and Embase (searched simultaneously via the Ovid SP platform)**

Term group	#	Terms
Disease area: advanced/ metastatic/non-resectable melanoma	1	exp Skin Neoplasms/
	2	exp Melanoma/
	3	exp skin tumor/
	4	Melanoma$.tw.
	5	((skin$ or melano$) adj3 (cancer$ OR carcinoma$ OR neoplas$ OR tumo?r$ OR malignanc$)).tw.
	6	Or/1-5
	7	(metastati$ OR metastasi$ OR advanced OR stage III OR stage 3 OR stage IIIa OR stage 3a OR stage IIIb OR stage 3b OR stage IIIc OR stage 3c OR stage IV OR stage 4 or non-resectable$ or nonresectable$ or unresectable$).tw.
	8	6 and 7
Drugs	9	(cobimetinib OR cotellic OR GDC-0973 OR XL518 OR XL-518)
	10	(dabrafenib OR tafinlar)
	11	(vemurafenib OR zelboraf)
	12	10 or 11
	13	9 and 12
RCTs	14	exp Randomized Controlled Trials as Topic/
	15	exp Randomized Controlled Trial/
	16	exp Random Allocation/
	17	exp Randomization/
	18	exp Double Blind Method/
	19	exp Single Blind Method/
	20	exp Cross-over Procedure/
	21	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
	22	exp Clinical Trial/
	23	Clinical trial, phase ii.pt.
	24	Clinical trial, phase iii.pt.
	25	Clinical trial, phase iv.pt.
	26	exp Phase 2 Clinical Trial/ or exp Clinical trial, phase II/
	27	exp Phase 3 Clinical Trial/ or exp Clinical trial, phase III/
	28	exp Phase 4 Clinical Trial/ or exp Clinical trial, phase IV/
	29	Controlled clinical trial.pt.
	30	Randomized controlled trial.pt.
	31	Multicenter study.pt.
	32	Clinical trial.pt.
	33	Comparative study.pt.
	34	exp Clinical Trials as Topic/
	35	trial$.ti.
	36	(clinical adj trial$).tw.
	37	exp Placebos/
	38	placebo$.ti,ab.
	39	randomly allocated.tw.
	40	(allocated adj2 random$).tw.
	41	random allocation.tw.
	42	random assignment.tw.
	43	randomi?ed.ti,ab.

Term group	#	Terms
	44	randomi?ation.tw.
	45	randomly.ti,ab.
	46	RCT.tw.
	47	Or/14-46
Exclusion terms	48	Animals/ not humans/
	49	(comment or editorial or "case reports" or "clinical trial, phase I").pt.
	50	(case stud$ or case report$).ti.
	51	Or/48-50
Combined	52	8 and 13 and 47
	53	52 not 51
	54	Remove duplicates from 53

-
- **Table 65. Search terms for the RCT search of Embase Alert (searched via the ProQuest platform)**

Term group	#	Terms
Disease area (advanced/ metastatic/non-resectable melanoma) and drugs	S1	EMB.EXACT.EXPLODE("melanoma")
	S2	MESH.EXACT.EXPLODE("Melanoma")
	S3	vemurafenib
	S4	dabrafenib
	S5	cotellic or cobimetinib OR GDC-0973 OR XL518 OR XL-518
	S6	S1 or S2
	S7	S3 or S4
	S8	S5 and S7
	S9	skin near/0 cancer
	S10	MESH.EXACT.EXPLODE("Neoplasm Metastasis")
	S11	EMB.EXACT.EXPLODE("metastasis")
	S12	metasta*
	S13	S10 or S11 or S12
	S14	S9 and S13
	S15	S6 or S14
	S16	S8 and S15
RCTs	S17	EMB.EXACT.EXPLODE("comparative study")
	S18	MESH.EXACT.EXPLODE("Comparative Study")
	S19	MESH.EXACT.EXPLODE("Multicenter Study")
	S20	EMB.EXACT.EXPLODE("multicenter study")
	S21	EMB.EXACT.EXPLODE("clinical trial")
	S22	MESH.EXACT.EXPLODE("Clinical Trial")
	S23	MESH.EXACT.EXPLODE("Randomized Controlled Trial")
	S24	EMB.EXACT.EXPLODE("randomized controlled trial")
	S25	EMB.EXACT.EXPLODE("meta analysis")
	S26	MESH.EXACT.EXPLODE("Meta-Analysis")
	S27	clinical trial
	S28	randomi?ed controlled trial
	S29	randomi?ed or randomi?ation
	S30	S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26
	S31	S27 and S29
	S32	S28 or S31
	S33	S30 or S32

Term group	#	Terms
Exclusion terms and combined	S34	(S16 and S33) NOT rtype.exact("Review" OR "Note" OR "Letter" OR "Editorial" OR "Short Survey" OR "Case Reports")

-

- **Table 66. Search terms for the RCT search of the Cochrane Library Databases (searched simultaneously via the Wiley Online platform)**

Term group	#	Terms
Disease area: advanced/ metastatic/non-resectable melanoma	1	MeSH descriptor **Skin Neoplasms** explode all trees
	2	MeSH descriptor **Melanoma** explode all trees
	3	Melanoma*
	4	(skin* or melano*) NEAR/3 (cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour* OR malignanc*)
	5	#1 OR #2 OR #3 OR #4
	6	(metastati* OR metastasi* OR advanced OR stage III OR stage 3 OR stage IIIa OR stage 3a OR stage IIIb OR stage 3b OR stage IIIc OR stage 3c OR stage IV OR stage 4 or non-resectable* OR nonresectable* OR unresectable*)
	7	#5 AND #6
Drugs	8	(cobimetinib OR cotellic OR GDC-0973 OR XL518 OR XL-518)
	9	(dabrafenib OR tafinlar)
	10	(vemurafenib OR zelboraf)
	11	#8 AND (#9 OR #10)
RCTs	12	MeSH descriptor **Randomized Controlled Trials as Topic** explode all trees
	13	MeSH descriptor **Randomized Controlled Trial** explode all trees
	14	MeSH descriptor **Random Allocation** explode all trees
	15	MeSH descriptor **Double Blind Method** explode all trees
	16	MeSH descriptor **Single Blind Method** explode all trees
	17	((singl* OR doubl* OR treb* OR tripl*) NEXT (blind* OR mask*))
	18	MeSH descriptor **Clinical Trial** explode all trees
	19	Clinical trial, phase ii:pt
	20	Clinical trial, phase iii:pt
	21	Clinical trial, phase iv:pt
	22	MeSH descriptor **Clinical trial, phase II** explode all trees
	23	MeSH descriptor **Clinical trial, phase III** explode all trees
	24	MeSH descriptor **Clinical trial, phase IV** explode all trees
	25	Controlled clinical trial:pt
	26	Randomized controlled trial:pt
	27	Multicenter study:pt
	28	Clinical trial:pt
	29	MeSH descriptor **Clinical Trials as Topic** explode all trees
	30	trial*:ti
	31	(clinical NEXT trial*)
	32	MeSH descriptor **Placebos** explode all trees
	33	placebo*:ti,ab
	34	“randomly allocated”
	35	(allocated NEAR/2 random*)
	36	“random allocation”

Term group	#	Terms
	37	“random assignment”
	38	randomi?ed:ti,ab
	39	randomi?ation
	40	randomly:ti,ab
	41	RCT
	42	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
Exclusion terms	43	MeSH descriptor **animals**
	44	MeSH descriptor **humans**
	45	#43 NOT #44
	46	(comment OR editorial OR "case reports" OR "clinical trial, phase I"):pt
	47	(case stud* OR case report*):ti
	48	#45 OR #46 OR #47
Combined	49	#7 AND #11 and #42
	50	#49 NOT #48

-
- **Table 67. Search terms for the RCT search of the congress proceedings**

Term group	#	Terms
Drugs	1	Cobimetinib
	2	Cotellic
	3	GDC-0973
	4	XL518
	5	XL-518

Appendix 3: Included relevant studies

A summary of the records included at the full-text review stage of the systematic review to identify RCT evidence is presented in Table 68, and those excluded are presented in Table 69.

Table 68. Records included in the systematic literature review of RCTs

Citation	RCT	Comments
Larkin 2014. "Combined vemurafenib and cobimetinib in BRAF-mutated melanoma." *New England Journal of Medicine.* 371(20):1867-1876.	CoBRIM	Primary data source; peer-reviewed publication.
Larkin 2015. "Update of progression-free survival (PFS) and correlative biomarker analysis from coBRIM: Phase III study of cobimetinib (cobi) plus vemurafenib (vem) in advanced BRAF-mutated melanoma." *American Society of Clinical Oncology Annual Meeting.*	CoBRIM	Secondary data source; congress proceeding reporting longer-term follow-up compared with the primary data source.
Dréno 2015. "Quality-of-life (QOL) assessment in patients (pts) with metastatic melanoma receiving vemurafenib (V) and cobimetinib (C)." *American Society of Clinical Oncology Annual Meeting.*	CoBRIM	Secondary data source; congress proceeding reporting patient-reported outcomes of quality of life in the coBRIM study.
De La Cruz-Merino 2015. "Clinical features of cobimetinib (COBI)–associated serous retinopathy (SR) in BRAF-mutated melanoma patients (pts) treated in the coBRIM study." *American Society of Clinical Oncology Annual Meeting.*	CoBRIM	Secondary data source; congress proceeding reporting on a specific adverse event in the coBRIM study – serous retinopathy.
Dréno 2014. "Incidence, course, and management of toxicities associated with vemurafenib and cobimetinib in the coBRIM study." *Society for Melanoma Research Congress.*	CoBRIM	Secondary data source; congress proceeding reporting on a toxicities in the coBRIM study.

Table 69. Records excluded at the full-text review stage of the SLR of RCTs

Citation	Study	Reason for exclusion
Han 2015. "Population pharmacokinetics and dosing implications for cobimetinib in patients with solid tumours." *American Society of Clinical Oncology Annual Meeting.*	CoBRIM	The outcomes reported were not of interest.
McArthur 2014. "LBA5_PR - Phase 3, double-Blind, placebo-controlled study of vemurafenib versus vemurafenib + cobimetinib in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma (NCT01689519)" *European Society for Medical Oncology.*	CoBRIM	The outcomes were subsequently published in a manuscript.
Xie 2015. "The efficacy and safety of the combination of anti-BRAF agent and MEK inhibitor in advanced melanoma patients with BRAF V600 mutation: A meta-analysis." *American Society of Clinical Oncology Annual Meeting.*	Systematic review and meta-analysis	The treatment combinations were grouped together rather than looking at the specific cobimetinib and vemurafenib combination.

Appendix 4: Search strategy for indirect treatment comparison

To identify relevant RCTs, the following databases were interrogated on the 7th April 2015:

- MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present (via OVID)
- Embase 1980 to present (via OVID)
- The Cochrane Library (with no study design filter), via the OVID platform, incorporating:
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
  - The HTA Database
  - Cochrane Database of Systematic Reviews (Cochrane Reviews)
  - Database of Abstracts of Reviews of Effects (DARE)
  - NHS Economic Evaluation Database (NHS EED)

Table 70 below shows the inclusion/exclusion criteria applied to the search, **Error! Reference source not found.** shows the search strings and Figure 35 the PRISMA flow diagram for search results.

Table 70 ITC systematic literature search: Inclusion exclusions criteria

Criterion	Description
Inclusion criteria	
Population	Treatment naïve adults with metastatic or unresectable stage IIIC and/or stage IV melanoma (where studies enrolled a mixed population, and the results for metastatic or unresectable stage IIIC and/or stage IV melanoma patients were not reported separately, at least 80% of the enrolled patients were required to be metastatic or present with unresectable stage IIIC and/or stage IV melanoma). Studies enrolling patients who had received prior treatment for an earlier stage of the disease, but who were treatment naïve when presenting with metastatic disease were eligible for inclusion.

Intervention/comparator	The following interventions were of primary interest for the clinical review (not restricted by dosage or mode or administration):
	• Cobimetinib in combination with vemurafenib
	• Targeted drugs
	  ◦ Cobimetinib
	  ◦ Dabrafenib
	  ◦ Pembrolizumab
	  ◦ Trametinib
	  ◦ Vemurafenib
	• Immunotherapy
	  ◦ IFN
	  ◦ Ipilimumab

Criterion	Description
Inclusion criteria	

	• Nivolumab
	• Chemotherapy
	  • Dacarbazine
	  • Temozolomide
	• Placebo
	Studies reporting on several other agents were also identified and tagged, but are not discussed in this report:
	• Carboplatin
	• Cisplatin
	• Carmustine
	• Lomustine
	• Vinblastin
	• Vindesine
	• Fotemustine
	• Bevacizumab
	• Paclitaxel

Outcomes	The primary outcomes of interest were:
	• Efficacy:
	  • Overall survival
	  • 1 year survival rate
	  • Progression free survival
	  • Time to progression
	  • Response rates (CR, PR, SD, PD)
	• Safety:
	  • All grade 3/4 AEs including but not limited to:
	  • Photosensitivity
	  • Rash
	  • Cutaneous SCC
	  • Skin papilloma
	  • Arthralgia
	  • Chills
	  • Pyrexia
	  • Diarrhoea
	  • Retinopathy
	  • Hypertension
	  • Increased blood creatine phosphokinase
	  • Decreased ejection fraction
	  • Acneiform rash
	• HRQoL

Study design	RCTS: • Any design • All phases
Countries	No restriction

Criterion	Description
Inclusion criteria	
Language	English: English abstracts of foreign publications were considered
Date of publication	No restriction
Publication status	Published studies and unpublished data were considered

Table 71. Embase search strategy 1980 to 2015 Week 14: accessed April 7th 2015

# ▲	Searches	Results
1	exp Melanoma/	106252
2	melanoma$.mp.	135722
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	29364
4	exp metastasis/dr, dt, th [Drug Resistance, Drug Therapy, Therapy]	47369
5	metasta*.mp.	561424
6	4 or 5	561923
7	or/1-3	156108
8	6 and 7	47945
9	dacarbazine/	15552
10	(DTIC or dacarbazin$).mp.	15931
11	temozolomide.mp. or temozolomide/	14615
12	(interferon or IFN).mp.	295415
13	interferon/	57069
14	ipilimumab/	3585
15	ipilimumab.mp.	3689
16	vemurafenib.mp. or vemurafenib/	3157
17	dabrafenib.mp. or dabrafenib/	1085
18	cobimetinib.mp. or cobimetinib/	111

# ▲	Searches	Results
19	nivolumab.mp. or nivolumab/	651
20	pembrolizumab.mp.	229
21	trametinib.mp. or trametinib/	988
22	cisplatin/ or Cisplatin.mp.	136827
23	Fotemustine.mp. or fotemustine/	1303
24	carboplatin/ or carboplatin.mp.	48849
25	vindesine/ or vindesine.mp.	7127
26	bevacizumab/ or bevacizumab.mp.	35604
27	paclitaxel/ or paclitaxel.mp.	74026
28	vinblastin/ or vinblastin.mp.	29419
29	lomustine/ or lomustine.mp.	8681
30	Carmustine/ or carmustine.mp.	15563
31	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	553397
32	Clinical trial/	841621
33	Randomized controlled trial/	365910
34	Randomization/	65569
35	Single blind procedure/	19865
36	Double blind procedure/	119111
37	Crossover procedure/	42140
38	Placebo/	253512
39	Randomi?ed controlled trial$.tw.	113106
40	Rct.tw.	16468
41	Random allocation.tw.	1391

# ▲	Searches	Results
42	Randomly allocated.tw.	21920
43	Allocated randomly.tw.	2005
44	(allocated adj2 random).tw.	720
45	Single blind$.tw.	15471
46	Double blind$.tw.	148632
47	((treble or triple) adj blind$).tw.	434
48	Placebo$.tw.	210965
49	Prospective study/	283180
50	or/32-49	1440651
51	Case study/	30987
52	Case report.tw.	277666
53	Abstract report/ or letter/	917925
54	or/51-53	1220430
55	50 not 54	1401825
56	8 and 31 and 55	2505

Table 72 MEDLINE search strategy Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present: accessed April 7th 2015

# ▲	Searches	Results
1	exp Melanoma/	75679
2	melanoma*.mp.	100291
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	23058
4	exp Neoplasm Metastasis/	160291

# ▲	Searches	Results
5	metasta*.mp.	400864
6	4 or 5	406766
7	1 or 2 or 3	117317
8	6 and 7	33209
9	Dacarbazine/	5518
10	(DTIC or dacarbazin$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6575
11	temozolomide.mp.	4160
12	Interferons/	19932
13	(interferon or IFN).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	178171
14	ipilimumab.mp.	990
15	vemurafenib.mp.	764
16	dabrafenib.mp.	283
17	cobimetinib.mp.	17
18	nivolumab.mp.	138
19	pembrolizumab.mp.	56
20	trametinib.mp.	193
21	cisplatin.mp. or Cisplatin/	56632
22	Fotemustine.mp.	341
23	carboplatin.mp. or Carboplatin/	13250
24	vindesine.mp. or Vindesine/	1761
25	bevacizumab.mp.	10563

# ▲	Searches	Results
26	paclitaxel.mp. or Paclitaxel/	26146
27	Vinblastine/ or vinblastin*.mp.	14978
28	lomustine.mp. or Lomustine/	1985
29	Carmustine.mp. or Carmustine/	4228
30	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	296382
31	Randomized controlled trials as Topic/	96265
32	Randomized controlled trial/	387943
33	Random allocation/	82347
34	Double blind method/	128277
35	Single blind method/	20035
36	Clinical trial/	491226
37	exp Clinical Trials as Topic/	286022
38	or/31-37	938678
39	(clinic$ adj trial$1).tw.	230077
40	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	133704
41	Placebos/	32669
42	Placebo$.tw.	164739
43	Randomly allocated.tw.	18227
44	(allocated adj2 random).tw.	719
45	or/39-44	440341
46	38 or 45	1103023
47	Case report.tw.	216288
48	Letter/	870258

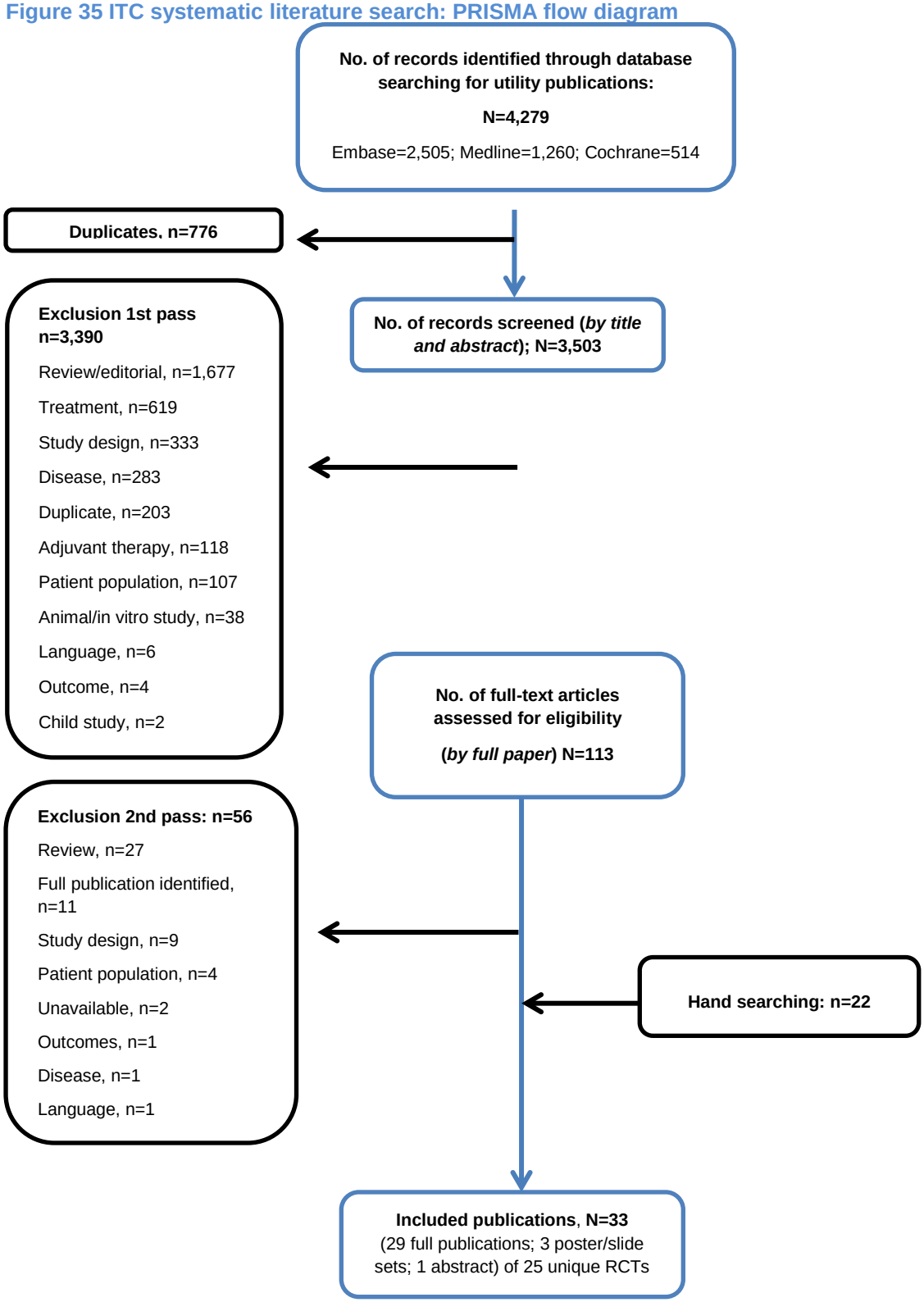
# ▲	Searches	Results
49	Historical article/	311494
50	Review of reported cases.pt.	0
51	Review, multicase.pt.	0
52	or/47-51	1385984
53	46 not 52	1073968
54	8 and 30 and 53	1260

Table 73 Cochrane library search strategy EBM Reviews - accessed April 7th 2015

#	Searches	Results
1	exp Melanoma/	1045
2	melanoma*.mp.	2313
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	963
4	exp Neoplasm Metastasis/	3512
5	metasta*.mp.	15996
6	4 or 5	16064
7	1 or 2 or 3	3011
8	6 and 7	1020
9	Dacarbazine/	432
10	(DTIC or dacarbazin$).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	784
11	temozolomide.mp.	310
12	Interferons/	280
13	(interferon or IFN).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	10977
14	ipilimumab.mp.	95
15	vemurafenib.mp.	30
16	dabrafenib.mp.	18

#	Searches	Results
17	cobimetinib.mp.	3
18	nivolumab.mp.	5
19	pembrolizumab.mp.	1
20	trametinib.mp.	18
21	cisplatin.mp. or Cisplatin/	7540
22	Fotemustine.mp.	31
23	carboplatin.mp. or Carboplatin/	2793
24	vindesine.mp. or Vindesine/	560
25	bevacizumab.mp.	1422
26	paclitaxel.mp. or Paclitaxel/	3680
27	Vinblastine/ or vinblastin*.mp.	1356
28	lomustine.mp. or Lomustine/	387
29	Carmustine.mp. or Carmustine/	459
30	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	25054
31	8 and 30	514

Figure 35 ITC systematic literature search: PRISMA flow diagram



Appendix 5: Methods, results, outcomes and quality assessment of the relevant trials in the ITC

Table 74 Study design and baseline characteristics for included studies in NMA

Study	Inclusion criteria	Details of previous treatment	Treatment arms	Number randomised	Male, n (%)	Age, median, years (range)	ECOG PS, n (%)			Duration of treatment, median (range) or (min, max)
							0	1	2	
Chapman et al, 2011 (5), Chapman et al, 2012 (4) and McArthur et al, 2014 (23) (BRIM-3) NCT01006980 Phase III RCT Multi-national (104 sites)	• Patients with unresectable previously untreated stage IIIC or stage IV melanoma tested positive for the BRAF V600E mutation • Age ≥18 years • Life expectancy ≥3 months • ECOG PS 0 or 1 • Adequate haematologic, renal and liver function as defined by laboratory values performed within 28 days prior to initiation of dosing	Patients were previously untreated	**VM monotherapy** (960 mg orally BD)	337	59	56	229 (68.0)	108 (32.0)	0 (0.0)	NR
			DTIC monotherapy (1,000 mg/m^2 IV infusion every 3 weeks)	338	54	52	230 (68.0)	108 (32.0)	0 (0.0)	
			DTIC (250 mg/m^2 as a 20 minute IV infusion, for 5 consecutive days, every 3 weeks) **plus TAM** (20	62	52	58	NR	NR	5/60 (8.0)	

Study	Inclusion criteria	Details of previous treatment	Treatment arms	Number randomised	Male, n (%)	Age, median, years (range)	ECOG PS, n (%)			Duration of treatment, median (range) or (min, max)
							0	1	2	
			mg/m^2 orally rounded to the nearest 10 mg)							
Flaherty et al, 2012a (11) NCT01072175 Open-label Phase II RCT (Part C) NR (16 sites)	• Patients aged ≥18 years with histologically confirmed metastatic melanoma with either BRAF V600 E of BRAF V600 K mutations • Measurable disease • ECOG PS 0/1 • Adequate organ function • Patients with treated brain metastases and at least a 3 month history of stable disease were eligible	Patients could have undergone no more than one previous chemotherapy regimen for advanced or metastatic melanoma; prior treatment with BRAF or MEK inhibitors was not permitted	**Dabrafenib monotherapy** 150 mg twice daily	54	29 (54.0)	50	34 (63.0)	20 (37.0)	NR	NR
			Dabrafenib 150 mg twice daily **plus trametinib** 1 mg/day	54	30 (56.0)	49	38 (70.0)	16 (30.0)	NR	
			Dabrafenib 150 mg twice daily **plus trametinib** 2 mg/day	54	34 (63.0)	58	35 (65.0)	19 (35.0)	NR	

Study	Inclusion criteria	Details of previous treatment	Treatment arms	Number randomised	Male, n (%)	Age, median, years (range)	ECOG PS, n (%)			Duration of treatment, median (range) or (min, max)
							0	1	2	
Flaherty et al, 2012b (12) NCT01245062 Open-label Phase III RCT Multi-national (103 sites)	• Patients with histologically confirmed, unresectable stage IIIC or IV cutaneous melanoma with a BRAF V600 E or K mutation • Age ≥18 years • Measurable disease • ECOG PS 0/1 • Adequate organ function	Patients could have received one previous chemotherapy regimen for advanced or metastatic melanoma; previous treatment with BRAF and MEK inhibitors and IPI was not permitted	**Trametinib monotherapy** 2 mg/day orally	214	120 (56.0)	55	136 (64.0)	78 (36.0)	NR	NR
			DTIC 1,000 mg/m^2 every 3 weeks **OR** p**aclitaxel** 175 mg/m^2 every 3 weeks	108	53 (49.0)	54	69 (64.0)	39 (36.0)	NR	
Hauschild et al, 2012 (14) and Hauschild et al, 2013 (13) (BREAK-3) NCT0122788	• Patients with histologically confirmed metastatic melanoma with BRAF V600E mutation • Age ≥18 years • ECOG PS 0 or 1 • Adequate	Patients were treatment naïve with the exception of IL-2, radiotherapy and surgery	**Dabrafenib monotherapy** (150 mg orally BD)	187	60	53	124 (66)	63 (33)	NR	Median time on study, 4.9 months

Study	Inclusion criteria	Details of previous treatment	Treatment arms	Number randomised	Male, n (%)	Age, median, years (range)	ECOG PS, n (%)			Duration of treatment, median (range) or (min, max)
							0	1	2	
9 Phase III RCT Multi-national (70 sites)	haematological, hepatic, renal and cardiac function		**DTIC monotherapy** (1,000 mg/m^2 IV every 3 weeks)	63	59	50	44 (70)	16 (25)	NR	
Larkin et al, 2014 (18) (coBRIM) NCT01689519 RCT Multi-national (135 sites)	• Patients with measurable disease, according to RECIST • ECOG PS 0 or 1 • Adequate hematologic, hepatic, renal, and cardiac function	Patients had received prior adjuvant therapy	**VM** (960 mg orally BD) **plus placebo**	248	56	55	164/244 (67)	80/244 (33)	0 (0)	NR
			VM (960 mg orally BD) **plus cobimetinib** (60 mg once daily for 21 days, followed by 7 days off)	247	59	56	184/243 (76)	58/243 (24)	1/243 (<1%)	
Long et al, 2014 (21), Long et al, 2015 (20) and Schadendorf et al, 2015	• Patients with histologically confirmed unresectable stage IIIC or IV, BRAF V600E/K mutant cutaneous metastatic	Patients were previously untreated for advanced or metastatic disease – study treatment was first-line	**Dabrafenib** (150 mg BD) plus t**rametinib** (2 mg/day)	211	111 (53)	55.0	155 (73)	55 (26)	NR	NR
			Dabrafenib (150 mg BD)	212	114	56.5	150	61	NR	

Study	Inclusion criteria	Details of previous treatment	Treatment arms	Number randomised	Male, n (%)	Age, median, years (range)	ECOG PS, n (%)			Duration of treatment, median (range) or (min, max)
							0	1	2	
(32) (COMBI-d) NCT01584648 Phase III RCT	melanoma • Age ≥18 years • ECOG PS ≤1 and		**plus placebo**		(54)		(71)	(29)		
Robert et al, 2015a (28) NCT01597908 Phase III open-label RCT Multi-national (193 sites)	• Previously untreated patients with unresectable stage IIIC or IV melanoma with BRAF V600E or V600K mutations • Measurable disease according to RECIST (version (1.1)) • ECOG PS 0 or 1	Patients were previously untreated	**Dabrafenib** (150 mg orally BD) **plus trametinib** (2 mg/day orally)	352	59	55	248/350 (71)	102/350 (29)	NR	Median exposure duration, 10 months
			VM monotherapy (960 mg orally BD)	352	51	54	248/352 (70)	104/352 (30)	NR	Median exposure duration, 6 months

Abbreviations: DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg; DTIC, dacarbazine; DTIC.FM, dacarbazine plus fotemustine; DTIC.IFN, dacarbazine plus interferon; ECOG PS, ECOG performance status; n, number of patients; NR, not reported; OS, overall survival; TM2mg, trametinib 2mg; VM, vemurafenib; VM.Cobi, vemurafenib plus cobimetinib

Table 75 Efficacy results of studies included in NMA

Study†	Regimens	N	PFS		OS	
			Months (95% CI) [IQR]	HR (95% CI), p value	Months (95% CI) [IQR]	HR (95% CI), p value
Chapman et al, 2011 (5) (BRIM-3) *Interim OS analysis (Dec 2010)*	**VM monotherapy** (960 mg orally BD)	337	5.3 (NR)	***0.26 (0.20 to 0.33) p<0.001*** *[favours VM monotherapy]*	NR	***0.37 (0.26 to 0.55) p<0.001*** *[favours VM monotherapy]*
	DTIC monotherapy (1,000 mg/m^2 IV infusion every 3 weeks)	338	1.6 (NR)		NR	
Chapman et al, 2012 (4) (BRIM-3) *Updated OS analysis (Nov 2011)*	**VM monotherapy** (960 mg orally BD)	337	NR	NR	13.2 (12.0, 15.0)	NR
	DTIC monotherapy (1,000 mg/m^2 IV infusion every 3 weeks)	338	NR		9.6 (7.9, 11.8)	
McArthur et al, 2014 (23) (BRIM-3) *Extended follow up (Feb 2012)*	**VM monotherapy** (960 mg orally BD)	337	6.9 (6.1, 7.0)	***0.38 (0.32, 0.46) p<0.0001*** *[favours VM monotherapy]*	13.6 (12.0, 15.2)	***0.70 (0.57, 0.87) p=0.0008*** *[favours VM monotherapy]*
	DTIC monotherapy (1,000 mg/m^2 IV infusion every 3 weeks)	338	1.6 (1.6, 2.1)		9.7 (7.9, 12.8)	
Flaherty et al, 2012a (11)	**Dabrafenib monotherapy** 150 mg twice daily	54	5.8 (4.6, 7.4)	Combination 150/1 vs dabrafenib: ***0.56 (0.37, 0.87) P=0.006*** *[favours combination 150/1]*	Not reached	NR

Study†	Regimens	N	PFS		OS	
			Months (95% CI) [IQR]	HR (95% CI), p value	Months (95% CI) [IQR]	HR (95% CI), p value
	Dabrafenib 150 mg twice daily **plus trametinib** 1 mg/day	54	9.2 (6.4, 11.0)	Combination 150/2 vs dabrafenib: ***0.39 (0.25, 0.62) P<0.001*** *[favours combination 150/2]*	Not reached	
	Dabrafenib 150 mg twice daily **plus trametinib** 2 mg/day	54	9.4 (8.6, 16.7)		Not reached	
Flaherty et al, 2012b (12)	**Trametinib monotherapy** 2 mg/day orally	214	4.8 (NR)	**0.45 (0.33, 0.63) p<0.001** *[favours trametinib monotherapy]*	Not reached	***0.54 (0.32, 0.92) p=0.01*** *[favours trametinib monotherapy]*
	DTIC 1,000 mg/m^2 every 3 weeks **OR paclitaxel** 175 mg/m^2 every 3 weeks	108	1.5 (NR)		Not reached	
Hauschild et al, 2012 (14) (BREAK-3) *Original analysis (Dec 2011)*	**Dabrafenib monotherapy** (150 mg orally BD)	187	5.1 (NR)	***0.30 (0.18, 0.51) P<0.0001*** *[favours dabrafenib monotherapy]*	NR	0.61 (0.25, 1.48) p value - NR *[favours dabrafenib monotherapy]*
	DTIC monotherapy (1,000 mg/m^2 IV every 3 weeks)	63	2.7 (NR)		NR	
Hauschild et al, 2013 (13) (BREAK-3)	**Dabrafenib monotherapy** (150 mg orally BD)	187	6.9 (NR)	NR	18.2 (16.6, NR)	0.76 (0.48, 1.21) P value – NR

Study†	Regimens	N	PFS		OS	
			Months (95% CI) [IQR]	HR (95% CI), p value	Months (95% CI) [IQR]	HR (95% CI), p value
Extended follow up (Jun/Dec 2012)	**DTIC monotherapy** (1,000 mg/m^2 IV every 3 weeks)	63	2.7 (NR)		15.6 (12.7, NR)	*[favours dabrafenib monotherapy]*
Larkin et al, 2014 (18) (coBRIM)	**VM** (960 mg orally BD) **plus placebo**	248	6.2 (5.6, 7.4)	***0.51 (0.39, 0.68) p<0.001*** *[favours VM + cobimetinib]*	Not reached	0.65 (0.42, 1.00) p=0.046
	VM (960 mg orally BD) **plus cobimetinib** (60 mg once daily for 21 days, followed by 7 days off)	247	9.9 (9.0, not reached)		Not reached	
Long et al, 2014 (21) (COMBI-d) *Interim OS analysis (cut-off not specified)*	**Dabrafenib** (150 mg BD) plus t**rametinib** (2 mg/day)	211	9.3 (NR)	***0.75 (0.57, 0.99) p=0.035*** *[favours dabrafenib + trametinib]*	NR	***0.63 (0.42, 0.94) p=0.023*** *[favours dabrafenib + trametinib]*
	Dabrafenib (150 mg BD) **plus placebo**	212	8.8 (NR)		NR	
Long et al, 2015 (20) (COMBI-d) *Final OS analysis (January 2015)*	**Dabrafenib** (150 mg BD) plus t**rametinib** (2 mg/day)	211	11.0 (8.0, 13.9)	***0.67 (0.53, 0.84) P<0.001*** *[favours dabrafenib + trametinib]*	25.1 (19.2, NR)	***0.71 (0.55, 0.92) P=0.011*** *[favours dabrafenib + trametinib]*
	Dabrafenib (150 mg BD) **plus placebo**	212	8.8 (5.9, 9.3)		18.7 (15.2, 23.7)	
Robert et al, 2015a (28)	**Dabrafenib** (150 mg orally BD) **plus trametinib** (2 mg/day orally)	352	11.4 (NR)	***0.56 (0.46, 0.69) p<0.001*** *[favours dabrafenib + trametinib]*	Not reached	***0.69 (0.53, 0.89) p=0.005*** *[favours dabrafenib + trametinib]*
	VM monotherapy (960 mg orally BD)	352	7.3 (NR)		17.2 (NR)	

Table 76 Quality Assessment of trials included in NMA

Study question	Chapman, 2011		Flaherty, 2012a		Flaherty, 2012b		Hauschild, 2012		Larkin, 2014		Long, 2015		McArthur, 2014		Robert, 2015a	
	How is the question addressed?	Grade (yes/no/not clear/NA)	How is the question addressed?	Grade (yes/no/not clear/NA)	How is the question addressed?	Grade (yes/no/not clear/NA)	How is the question addressed?	Grade (yes/no/not clear/NA)	How is the question addressed?	Grade (yes/no/not clear/NA)	How is the question addressed?	Grade (yes/no/not clear/NA)	How is the question addressed?	Grade (yes/no/not clear/NA)	How is the question addressed?	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	NR	Not clear	NR	Not clear	NR	Not clear	"A centrally located, computerised, interactive, voice activated response system controlled assignment of patient treatment"	Yes	NR	Not clear	"A centrally located, computerised, interactive, voice activated response system controlled the random assignment"	Yes	"Patients were randomly assigned using an interactive voice recognition system"	Yes	NR	Not clear
Was the concealment of	NR	Not clear	NR	Not clear	NR	Not clear	Randomisation system	Yes	NR	Not clear	Randomisation was	Yes	Randomisation was	Yes	NR	Not clear

treatment allocation adequate?							was centrally located				centrally located		supported by an independent vendor			
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	"Baseline characteristics of the patients were well balanced"	Yes	NR	Not clear	"Baseline characteristics of the patients were well-balanced between the two study groups"	Yes	"Treatment groups were well balanced for age, sex, race and disease status"	Yes	"The characteristics of the patients at baseline were generally well balanced between the two study groups"	Yes	"The treatment groups were well balanced for age, sex, ECOG performance status, lactate dehydrogenase, and M stage"	Yes	"the dacarbazine and vemurafenib groups were well balanced when examined as either a total randomised population (table 1) or as patients receiving randomised treatment"	Yes	"Known prognostic measures were well balanced in the two groups except for sex (59% men in the combination-therapy group vs. 51% in the vemurafenib group)"	Yes
Were the care providers, participants and	NR	Not clear	Open-label trial design	No	Open-label trial design	No	Open-label trial design; a masked independent	No	A blinded, independent central review	Not clear	Double-blind trial design	Yes	"Patients and investigators were aware of	No	Open-label trial design	No

outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?							review committee reviewed all scans and, per protocol, had to confirm progression before patients crossed over from dacarbazine to dabrafenib		of tumour assessments was performed				treatment allocation"			
Were there any unexpected imbalances in drop-outs between groups? If so, were	"A total of 118 patients had died at the time of the interim analysis. The data and safety monitori	Yes - explained	NR	Not clear	NR	Not clear	Discontinuations explained in study flow diagram (Figure 1)	No	NR	Not clear	Only one patient lost to follow up	No	NR	Not clear	2 patients in the combination arm and 3 in the VM arm did not receive study treatme	No

they explained or adjusted for?	ng board determined that both the overall survival and progression-free survival end points had met the prespecified criteria for statistical significance in favour of vemurafenib"														nt	
Is there any evidence to suggest that the authors measured more outcome	All outcomes stated in methods were reported in results section	No	All outcomes stated in methods were reported in	No	All outcomes stated in methods were reported in results section	No	All outcomes stated in methods were reported in results section	No	All outcomes stated in methods were reported in results section	No	All outcomes stated in methods were reported in results section, withdraw	No	All outcomes stated in methods were reported in results section	No	All outcomes stated in methods were reported in results	No

s than they reported?			results section							als of consent were similar between treatment arms				section	
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 analyses were performed in the intention-to-treat population"	Yes	Efficacy analyses were conducted on an ITT basis	Yes	Efficacy analyses were performed for the ITT and primary efficacy population	Yes	"All randomised patients were included in efficacy analyses; safety analyses included all randomised patients who received at least one dose of study medication"	Yes	"All the efficacy analyses were carried out in the intention-to-treat population"	Yes	All randomised patients were included in the ITT analysis	Yes	An ITT analysis of OS was conducted	Yes	"The interim analysis for overall survival was performed in the intention-to-treat population"	Yes
Overall risk of bias	**High**		**High**		**High**		**High**		**Unclear**		**Low**		**High**		**High**	

Appendix 6: Diagnostic plots for NMA treatment effect scales

Table 77 Explanation of NMA treatment effect scale diagnostic plots

	Diagnostic plot	**Demonstration of assumption hold**
PH model	Log cumulative hazards	Parallel lines in the log cumulative hazards plot
AFT model	Quantile-quantile (Q-Q) time to event	Straight line passes through the origin of the Q-Q plot

Figure 36 Log cumulative hazard vs log time for OS obtained from the current analysis

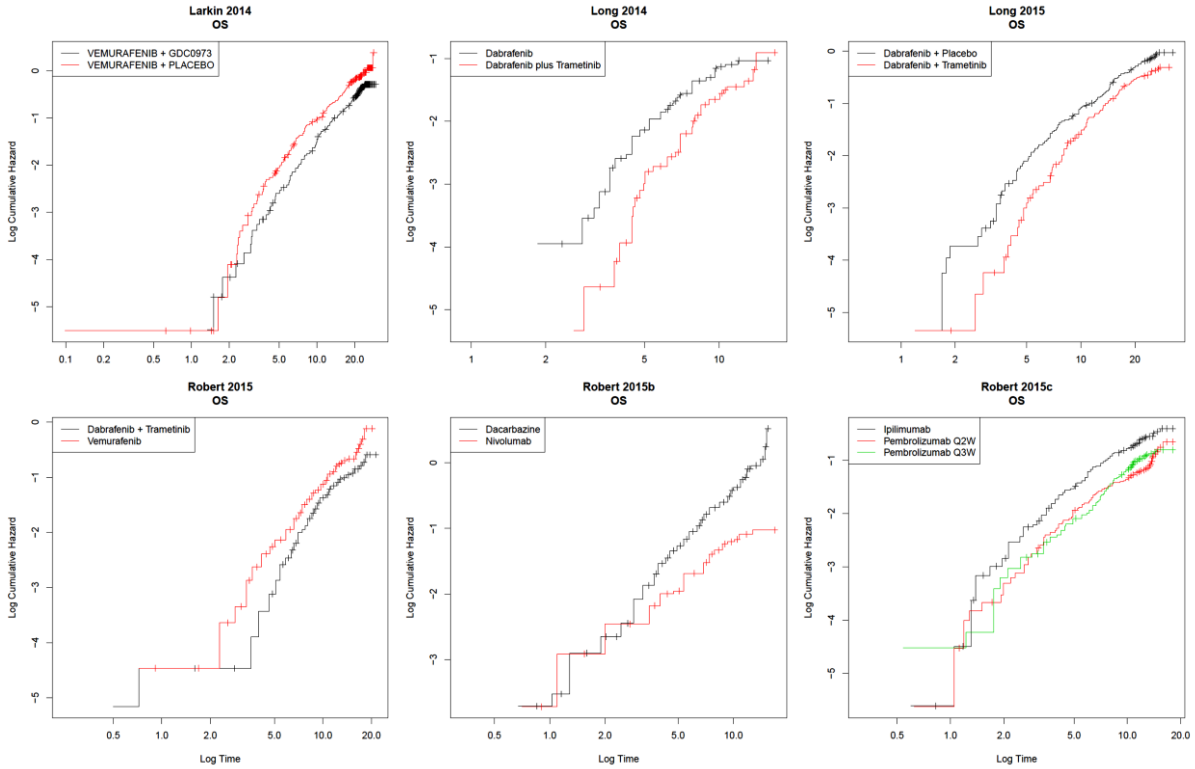


Figure 37 Log cumulative hazard vs log time for PFS obtained from the current analysis

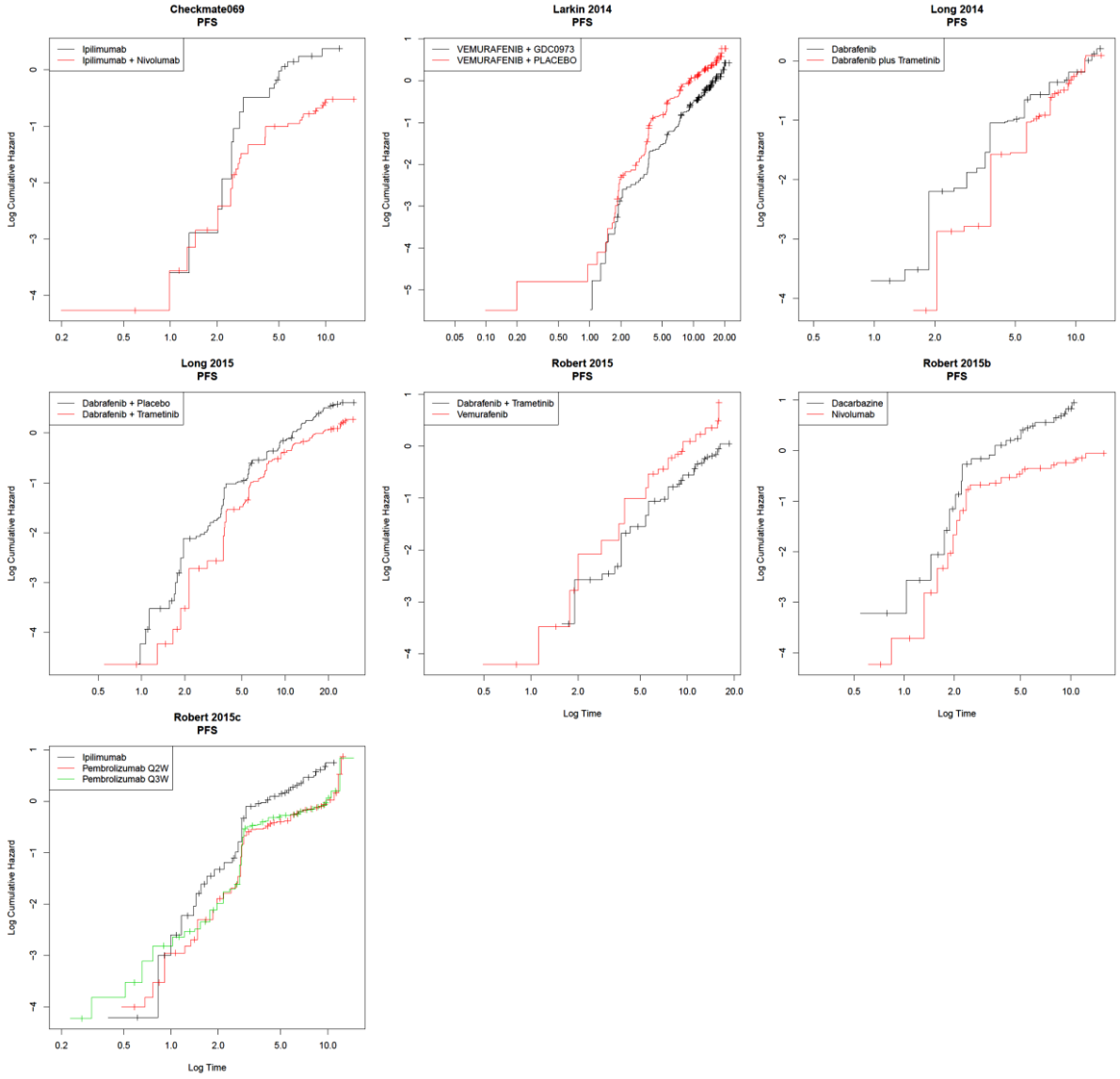


Figure 38 Q-Q plot for OS obtained from the current analysis

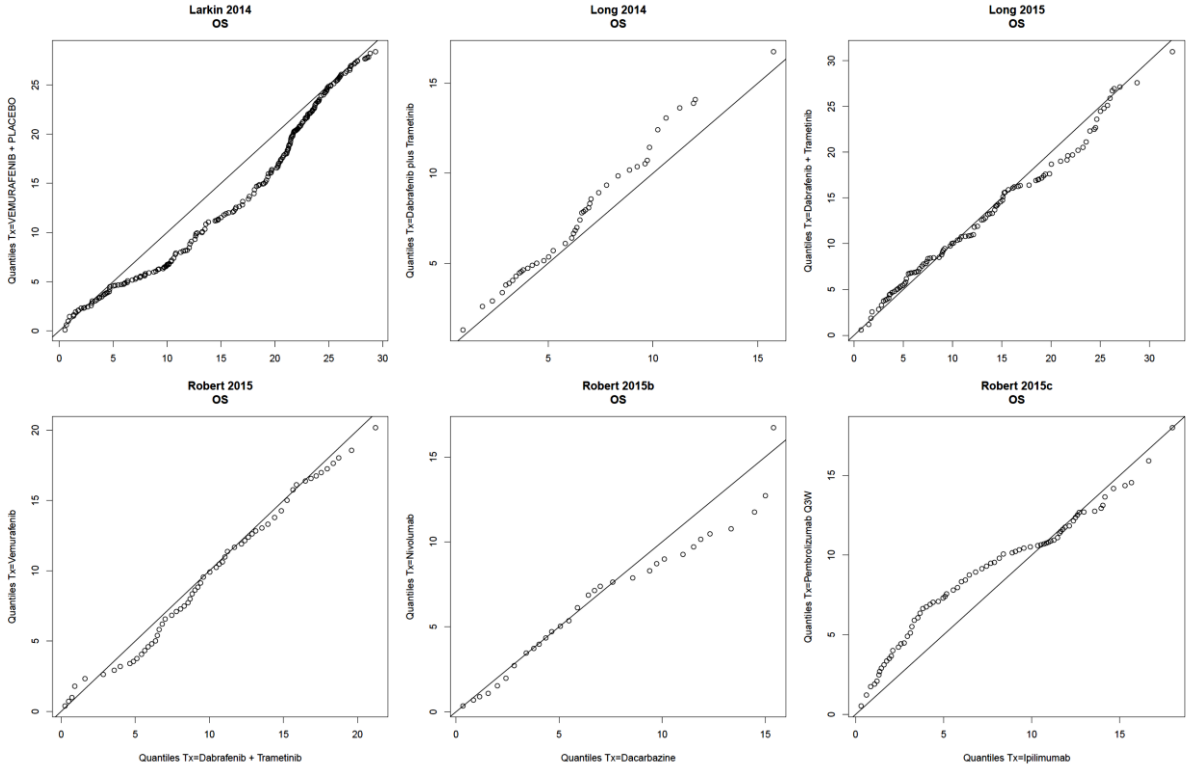
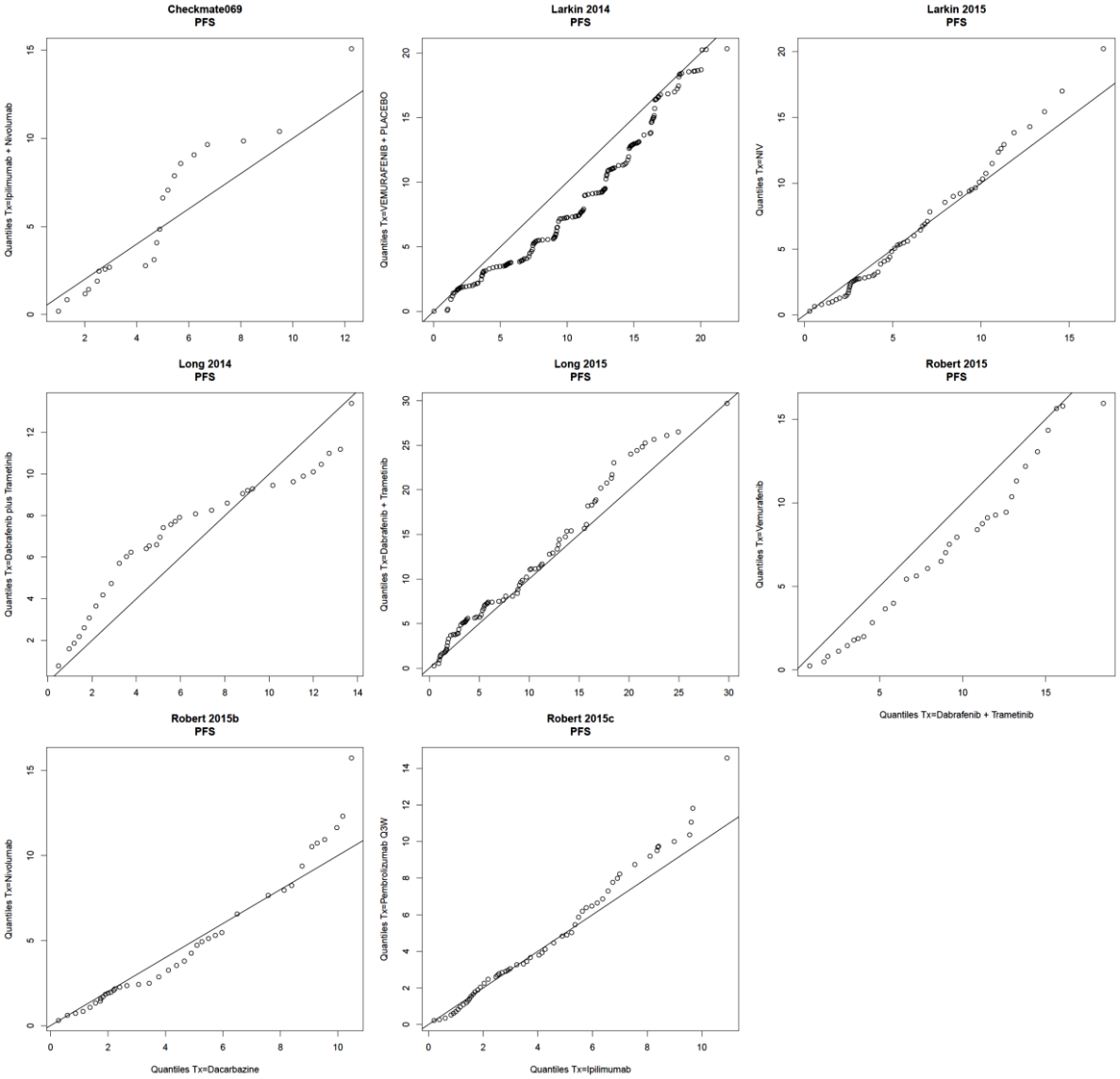


Figure 39 Q-Q plot for PFS obtained from the current analysis



Appendix 7: Recreating individual patient data to estimate AF

Individual patient data was recreated done using the algorithm published by Guyot et al. (2012). The algorithm recreates IPD based on scans of the published KM plots. Where available, data on the number of patients at risk at each time point is incorporated when applying the algorithm.

For the AFT model, generalised gamma survival models were fitted to each set of IPD using the function *flexsurvreg* with the option *gengamma* from the *flexsurv* package in R. The resulting set of log acceleration factors and standard errors were incorporated into the NMA. The inverse of the acceleration factor is reported: 1/AFT of 1 indicates there is no difference between the treatment and control, 1/AFT < 1 favours treatment, 1/AFT >1 favours control.

Table 78 HR and AFT calculated from IPD and published HR with 95% CI for OS

Study	Treatment	Baseline treatment	Published HR (95% CI)	HR (95% CI)	1/AFT (95% CI)
Flaherty et al, 2012a (15)	Dabrafenib + trametinib 1mg	Dabrafenib	NR	0.95 (0.49, 1.82)	1.01 (0.69, 1.46)
	Dabrafenib + trametinib 2mg	Dabrafenib	NR	0.70 (0.35, 1.39)	0.81 (0.56, 1.19)
Flaherty et al, 2012b (16)	Trametinib 2mg	Dacarbazine	0.54 (0.30, 0.92)	0.56 (0.35, 0.90)	0.64 (0.44, 0.93)
Hauschild et al, 2013 (17) (BREAK-3)	Dabrafenib	Dacarbazine	0.76 (0.48, 1.21)	0.79 (0.51, 1.21)	0.87 (0.62, 1.22)
Larkin et al, 2014 (4) (CoBRIM)	Vemurafenib	Vemurafenib + cobimetinib	1.54 (1.00, 2.38)	1.44 (1.12, 1.84)	1.37 (1.12, 1.68)
Long et al, 2015 (23) (COMBI-d)	Dabrafenib + trametinib 2mg	Dabrafenib	0.71 (0.55, 0.92)	0.74 (0.57, 0.96)	0.72 (0.57, 0.90)
McArthur 2014 (26) (BRIM-3)	Vemurafenib	Dacarbazine	0.70 (0.57, 0.87)	0.79 (0.66, 0.95)	0.65 (0.53, 0.79)
Robert et al, 2015a (31)	Vemurafenib	Dabrafenib + trametinib 2mg	1.45 (1.12, 1.89)	1.38 (1.06, 1.80)	1.26 (1.05, 1.50)

Appendix 8: Programming language used in the analysis

```
#BUGS code

#Arm-based parametrization (Hawkins et al., 2015)

#Network meta-analysis on the log hazard scale and the log inverse Accelerated Failure Time scale (AFT)

#Hazard Ratio (HR) and AFT obtained from recreated IPD (Guyot et al., 2012)

#Cox proportional hazards model fitted with coxph function of the survival R package

#AFT model fitted based on generalised gamma survival function using flexsurvreg R function with the option gengamma in the flexsurv package



#Data manipulation: convert the contrast statistics to arm-level statistics (Hawkins et al., 2015)

#based on log HR, standar deviation of log HR /log inverse AFT, standar deviation of log inverse AFT

#for multi-arms solve a simulaneous equation system using the variance-covariance matrix of the contrast from the cox or the generalise gamma model (Hawkins et al., 2015)

#NB. estimated standard errors are treated as true standard errors



#ns: Number of studies

#nt: Number of treatments

#nObs: Number of observations

#sd: Random effects standard deviation
```

```
#Fixed effects

model{


 #prior on treatment effect


 d[1] <- 0

   expD[1] <- exp(0)

 #prior on treatment effect mean

 for (tt in 2:nt){

          d[tt]~dnorm(0,1.0E-4)

        expD[tt] <- exp(d[tt])


 }

 #define prior on intercept

 for(ss in 1:ns){

  mu[ss] ~ dnorm(0,1.0E-4)

 }


 #fit data

 for(ii in 1:nObs ){

  x[ii] <- mu[study[ii]] + d[t[ii]]
```

```
  prec[ii] <- 1/(se[ii]*se[ii])
  #normal likelihood
  mn[ii] ~ dnorm(x[ii], prec[ii])
 }
}

#Random Effects with constant variance

model{

 #prior on random treatment effect variance
 sd~dunif(0,1)
 reTau <- 1/pow(sd,2)

 #prior on treatment effect

 d[1] <- 0
   expD[1] <- exp(0)
 #prior on treatment effect mean
```

```
for (tt in 2:nt){

        d[tt]~dnorm(0,1.0E-4)



     expD[tt] <- exp(d[tt])

}




#define prior on intercept

for(ss in 1:ns){

 mu[ss] ~ dnorm(0,1.0E-4)

 for (tt in 1:nt){

  re[ss,tt] ~dnorm(0,reTau)

 }

}







#fit data

for(ii in 1:nObs ){

 x[ii] <- mu[study[ii]] + d[t[ii]]
```

```
 + re[study[ii],t[ii]]

  prec[ii] <- 1/(se[ii]*se[ii])

  #normal likelihood

  mn[ii] ~ dnorm(x[ii], prec[ii])

 }

}
```

#Bibliography

#Hawkins, N., Scott, D. A., and Woods, B. (2015) 'Arm-based' parameterization for network meta-analysis. Res. Syn. Meth., doi: 10.1002/jrsm.1187. pdf

#Guyot, P., Ades, A. E., Ouwens, M. J., & Welton, N. J. (2012). Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology, 12(1), 9.

Appendix 9: Search strategy for cost-effectiveness studies

The following electronic data sources were searched for articles published between 1 January 2000 and 9 December 2015 (no start date to 10 December 2015 for EconLit):

1. MEDLINE® In-process & Other Non-indexed Citations and OVID MEDLINE1946–present
2. Embase 1974–present
3. Cochrane Library, comprising:
    a. Cochrane Database of Systematic Reviews (CDSR)
    b. Database of Abstracts of Reviews of Effects (DARE)
    c. Cochrane Central Register of Controlled Trials (CENTRAL)
    d. Cochrane Methodology Register (CMR)
    e. NHS Economic Evaluations Database (NHS EED)
    f. American College of Physicians (ACP) journal club
    g. Health technology Assessment (HTA)
4. EconLit 1866–present

Proceedings from the following congresses over the past 3 years (2013–2015) were interrogated for relevant abstracts:

1. International Society For Pharmacoeconomics and Outcomes Research (ISPOR) (US and European): http://www.ispor.org
2. American Society of Clinical Oncology (ASCO): http://www.asco.org/meetings
3. European Society for Medical Oncology (ESMO): http://www.esmo.org/
4. Society of Melanoma Research (SMR): http://www.societymelanomaresearch.org

Manufacturer submissions and evidence review group/assessment reports from the NICE were reviewed for additional economic data:

1. NICE: https://www.nice.org.uk

The additional sources were also hand searched:

1. Cost-effectiveness Analysis (CEA) Registry: https://research.tufts-nemc.org/cear4/
2. Research Papers in Economics (RePEc): http://repec.org/docs/RePEcIntro.html
3. Reference lists of included studies

Search strings are found in Table 79, Table 80, Table 81.and Table 82. Inclusion and exclusion criteria applied to the search results are found in Table 83. Table 84 shows results fitting the inclusion critera, but considered not relevant to the appraisal.

Table 79 Embase search for economic evaluations: Run 9th December 2015

#	Searches	Results
1	exp Melanoma/	117 150
2	melanoma$.mp.	149 305
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	32 208
4	or/1-3	171 596
5	cobimetinib.mp. or cobimetinib/	189
6	vemurafenib.mp. or vemurafenib/	3860
7	dabrafenib.mp. or dabrafenib/	1453
8	or/5-7	4333
9	Economic evaluation/	11 174
10	Socioeconomics/	119 679
11	Economic aspect/	106 467
12	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	24 656
13	Cost effectiveness analysis/	111 000
14	Cost minimization analysis/	2745
15	Cost benefit analysis/	70 499
16	Cost utility analysis/	6477
17	Cost consequence analysis/	11
18	(CEA or CMA or CBA or CUA or CCA).mp.	53 963
19	or/9-18	451 118
20	4 and 8 and 19	74
21	(animals not (humans and animals)).mp.	628 878
22	20 not 21	74
23	limit 22 to yr="2000 -Current"	74

Table 80 MEDLINE search for economic evaluations: Run 9th December 2015

#	Searches	Results
1	exp Melanoma/	80 769
2	melanoma$.mp.	107 356
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	24 284
4	or/1-3	125 199
5	cobimetinib.mp.	30
6	vemurafenib.mp.	995
7	dabrafenib.mp.	410
8	or/5-7	1187
9	Socioeconomic Factors/	125 722
10	Economic aspect.mp.	152
11	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	12 713
12	Cost effectiveness analysis.mp.	6686
13	Cost minimization analysis.mp. or "Costs and Cost Analysis"/	44 061
14	Cost benefit analysis/	65 334
15	Cost utility analysis.mp.	1557
16	Cost consequence analysis.mp.	84
17	(CEA or CMA or CBA or CUA or CCA).mp.	53 070
18	or/9-17	290 909
19	4 and 8 and 18	6
20	(animals not (humans and animals)).mp.	4 050 526
21	19 not 20	6
22	limit 21 to yr="2000 -Current"	6

Table 81 Cochrane Library search for economic evaluations:, ran 9 December 2015

#	Searches	Results
1	exp Melanoma/	1077
2	melanoma$.mp.	2540
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or	808

	adenocarcinoma$ or tumour$)).ti,ab.	
4	or/1-3	3115
5	cobimetinib.mp.	3
6	vemurafenib.mp.	42
7	dabrafenib.mp.	30
8	or/5-7	63
9	Socioeconomic Factors/	2202
10	Economic aspect.mp.	225
11	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	21 601
12	Cost effectiveness analysis.mp.	12 574
13	Cost minimization analysis.mp. or "Costs and Cost Analysis"/	3954
14	Cost benefit analysis/	16 557
15	Cost utility analysis.mp.	3669
16	Cost consequence analysis.mp.	122
17	(CEA or CMA or CBA or CUA or CCA).mp.	1542
18	or/9-17	33 293
19	4 and 8 and 18	5
20	(animals not (humans and animals)).mp.	1516
21	19 not 20	5
22	limit 21 to yr="2000 -Current" [Limit not valid in DARE; records were retained]	5

Table 82 EconLit search for economic evaluations, run 10th December 2015

#	Searches	Results
1	melanoma$.mp.	13
2	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	22
3	1 or 2	32

Table 83 Economic evaluation search inclusions and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Advanced (unresectable or metastatic)	Early stage melanoma or *BRAF*

	BRAF V600 mutation-positive melanoma[a]	V600 mutation-negative melanoma
Interventions	Any two of the following:[b] • Pre-progression • Dabrafenib • Vemurafenib • Cobimetinib in combination with vemurafenib	Other
Outcomes	Incremental cost-effectiveness/cost–utility ratios (ICERs/ICURs) Life-years, quality-adjusted life-years (QALYs) Total costs	Other
Study design	Cost-effectiveness analyses (CEA) Cost–utility analyses (CUA) Cost–benefit analyses (CBA) Cost-minimization analyses (CMA)	Cost and resource use studies
Date restrictions	1 January 2000 to 9 December 2015	
Language restrictions	English language	Non-English languages
Publication type	Primary paper, congress abstracts	Review, editorial, letter

[a]If the study enrolled a mixed population and the results for the metastatic or unresectable stage IIIc and/or stage IV melanoma population are not reported separately, at least 80% of the enrolled patients were metastatic or present with unresectable stage IIIc and/or stage IV melanoma.
[b]Economic evaluations that assessed cobimetinib in combination with vemurafenib vs any comparator were considered relevant to inform the HTA. Publications that met the inclusion criteria of the SR but were not considered relevant to support the submission are listed below.

Figure 40 Economic evalution search: PRISM flow diagram

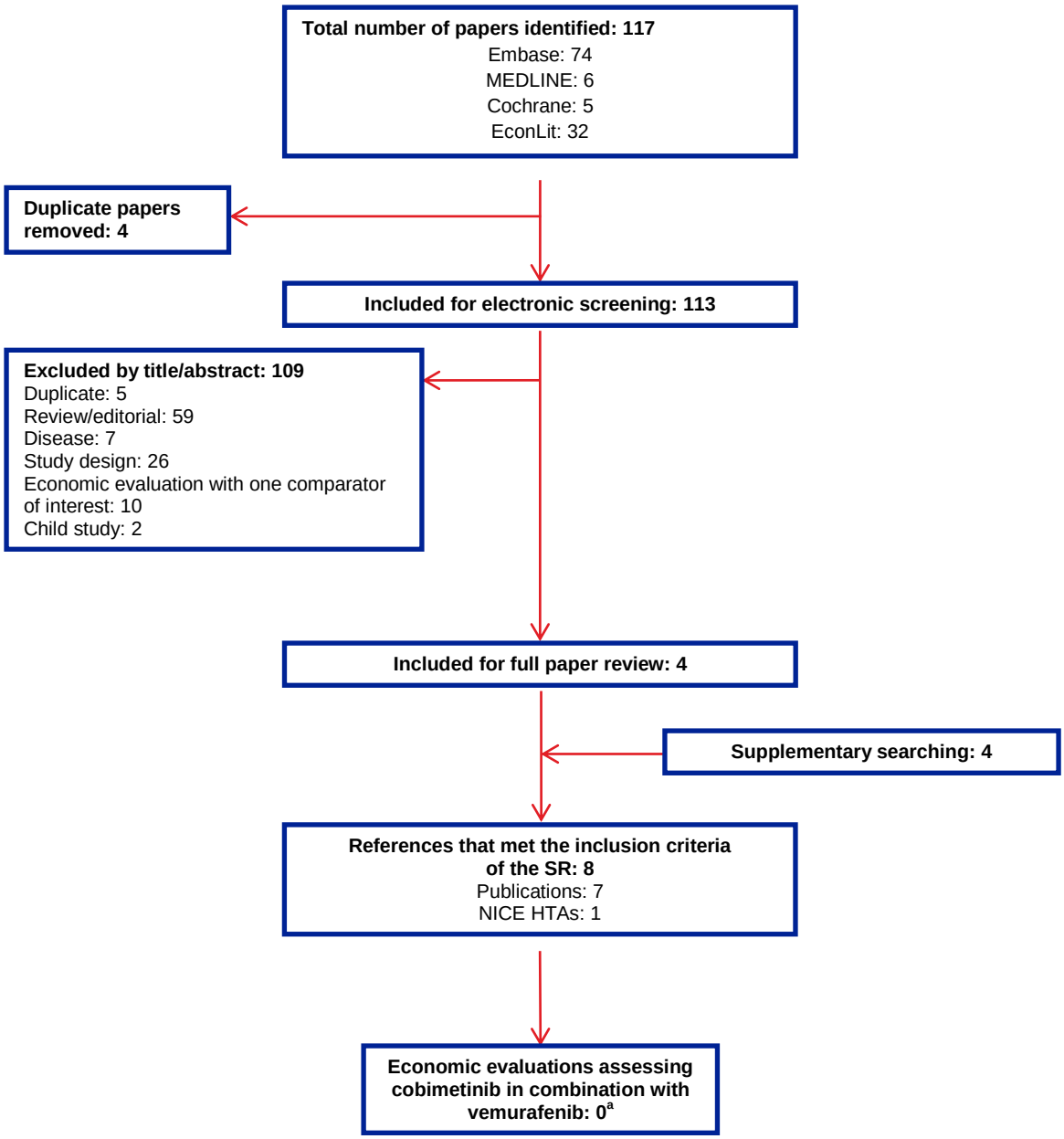


Table 84 Search results fitting criteria but not relevant to submission. rationale

Reference	Year	Country	Cost effectiveness comparators	Reason for omission from HTA document
Cinfio *et al.,* (2015) (Abstract)	2015	USA	Dabrafenib + trametinib combination, vemurafenib, dabrafenib, trametinib	Comparison not of interest
Delea *et al.,* (2015) (Full publication)	2015	Canada	Dabrafenib, dacarbazine, vemurafenib	Comparison not of interest
Fleeman *et al.,* (2015) (Full publication)	2015	UK	Vemurafenib, dacarbazine	Comparison not of interest
Hren, (2014) (Abstract)	2014	Slovenia	Vemurafenib, dacarbazine	Comparison not of interest

Liu and Rao, (2015) (Abstract)	2015	USA	Dabrafenib + trametinib combination, vemurafenib, dabrafenib, trametinib	Comparison not of interest
NICE, (2014) (TA321)	2014	UK	Dabrafenib, dacarbazine, vemurafenib	Comparison not of interest
Shih *et al.*, (2015) (Full publication)	2015	USA	Dabrafenib, dacarbazine, vemurafenib	Comparison not of interest
Shih *et al.,* (2014) (Abstract)	2014	USA	Dabrafenib, dacarbazine, vemurafenib	Comparison not relevant

Appendix 10: Parametric survival curve fitting

This appendix contains the alternative curve fits available for application in the economic model. These curve fits are for the following survival outcomes:

- OS
- PFS

PFS

Figure 41 PFS – Loglogistic (base case)

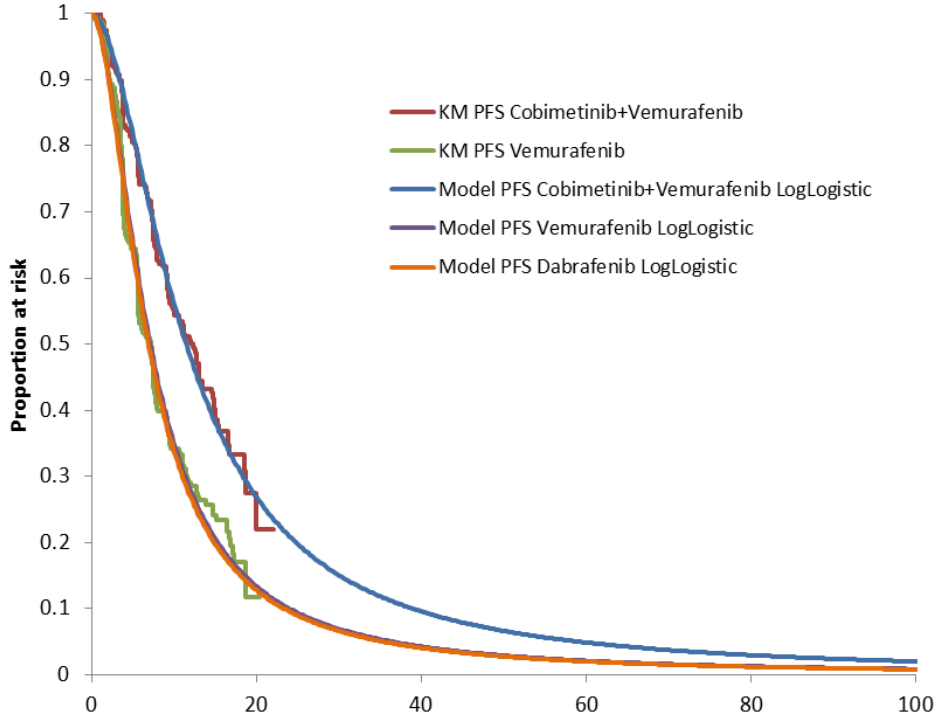


Figure 42 PFS - Expoential

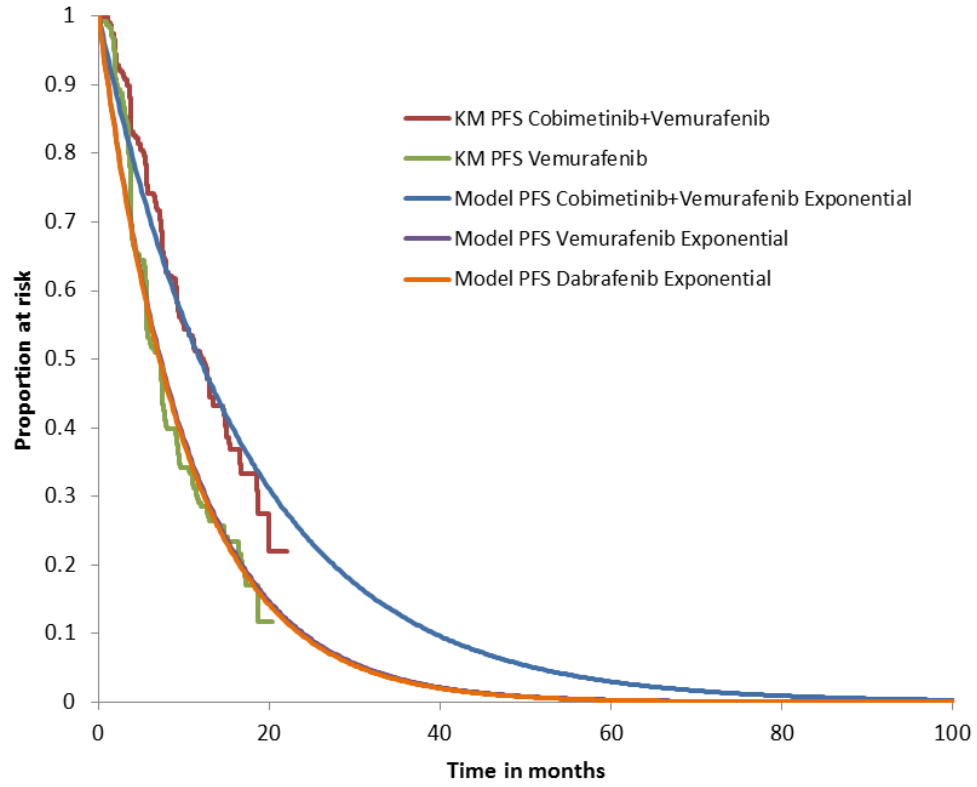


Figure 43PFS - Weibull

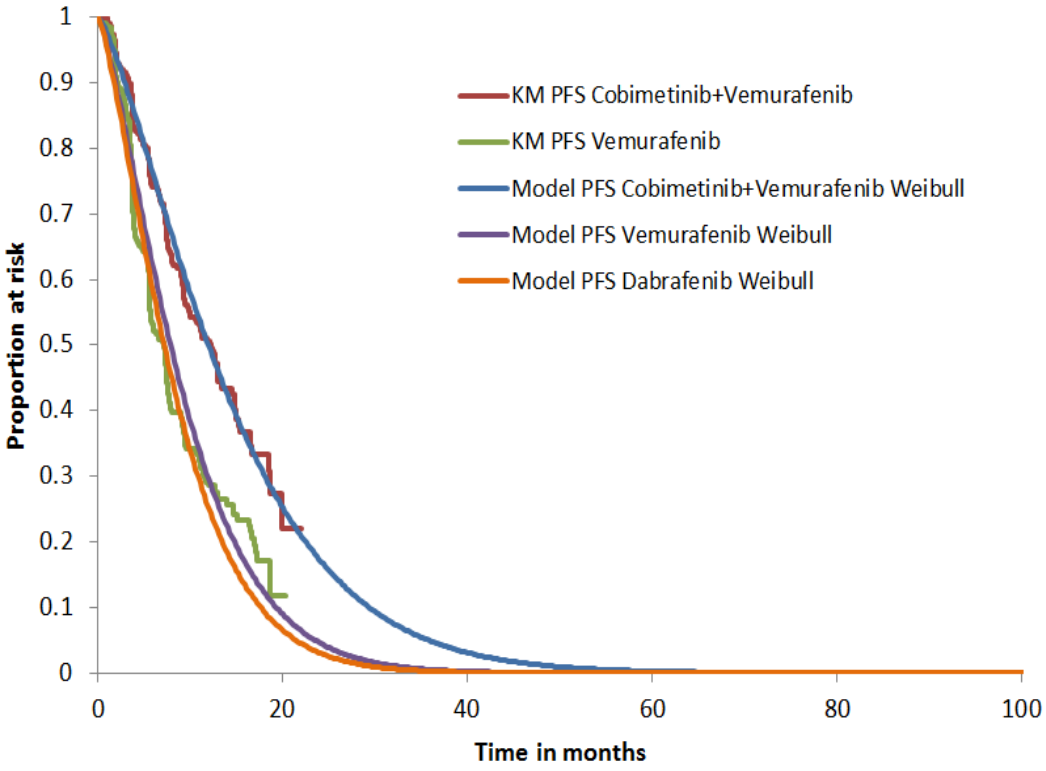


Figure 44 PFS - LogNormal

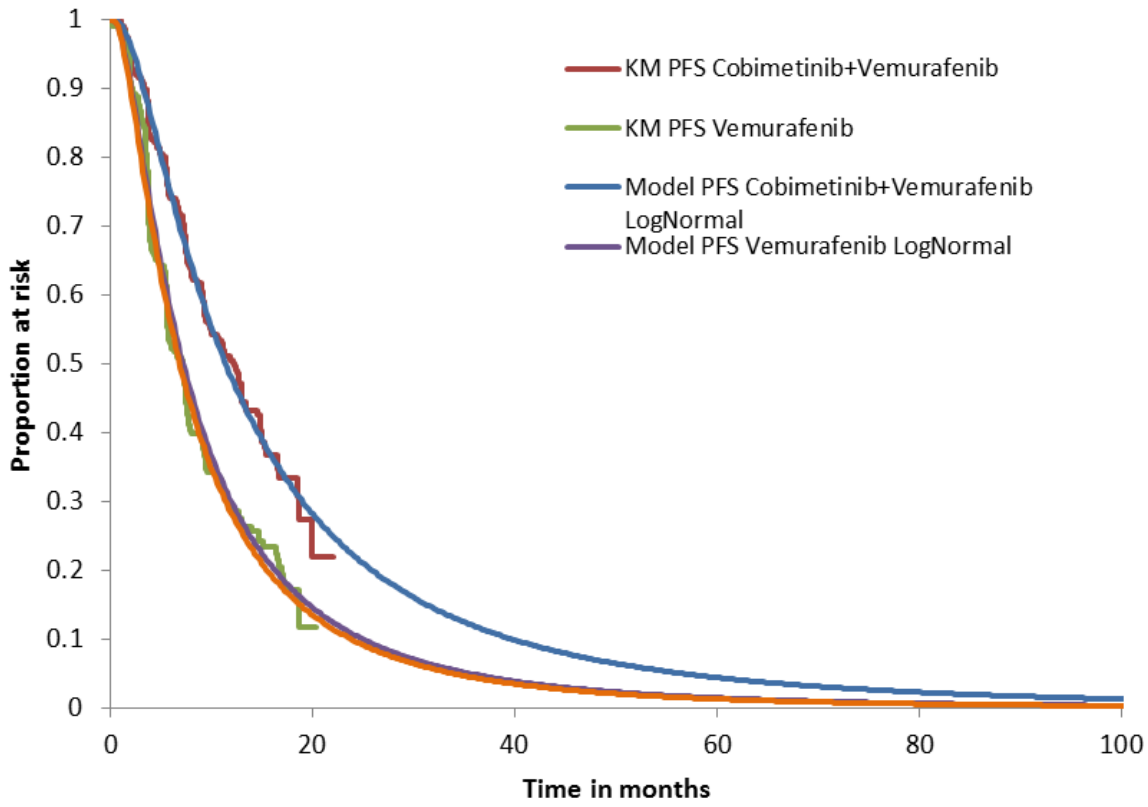


Figure 45 PFS - Gamma

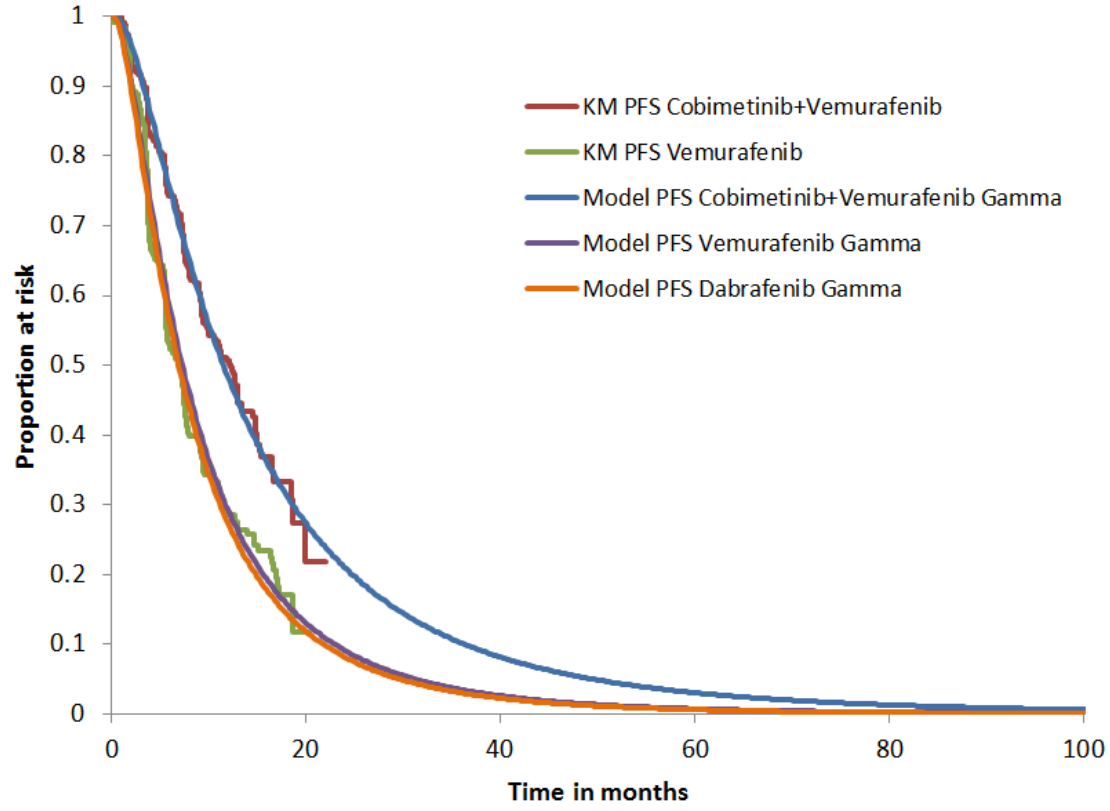
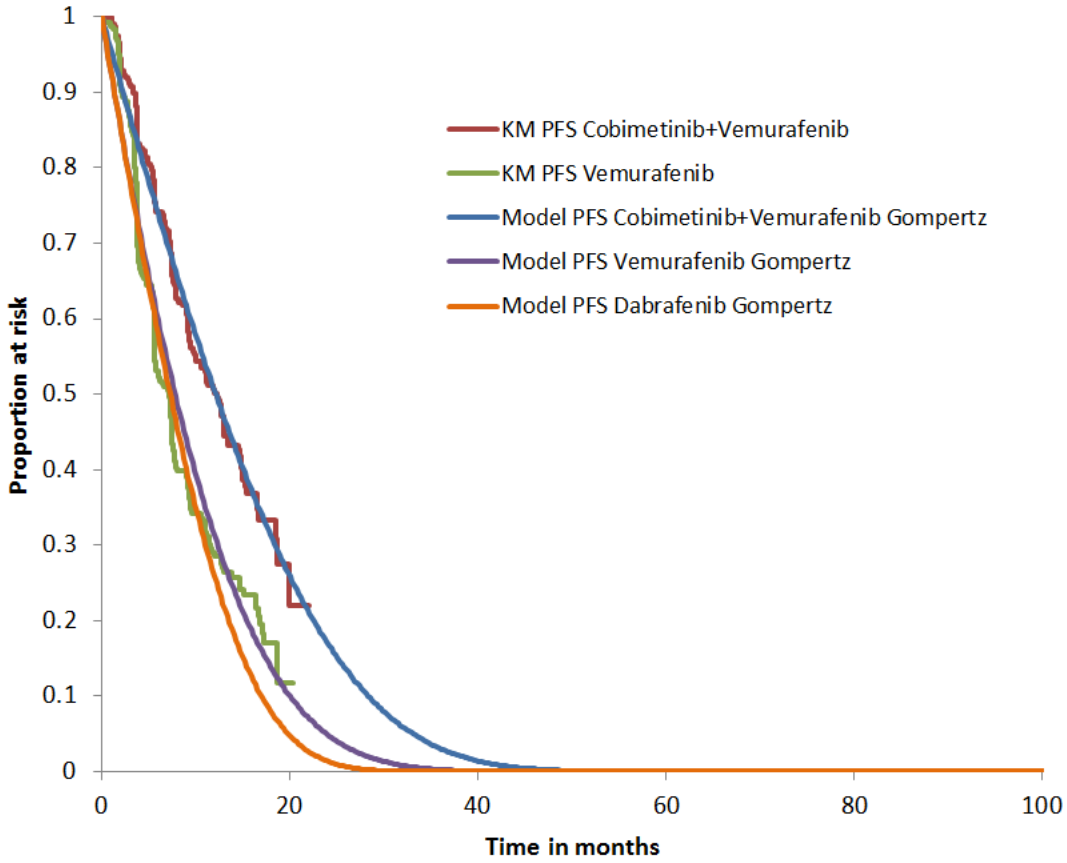


Figure 46 PFS - Gompertz



OS

Figure 47 OS - LogNormal (Base Case)

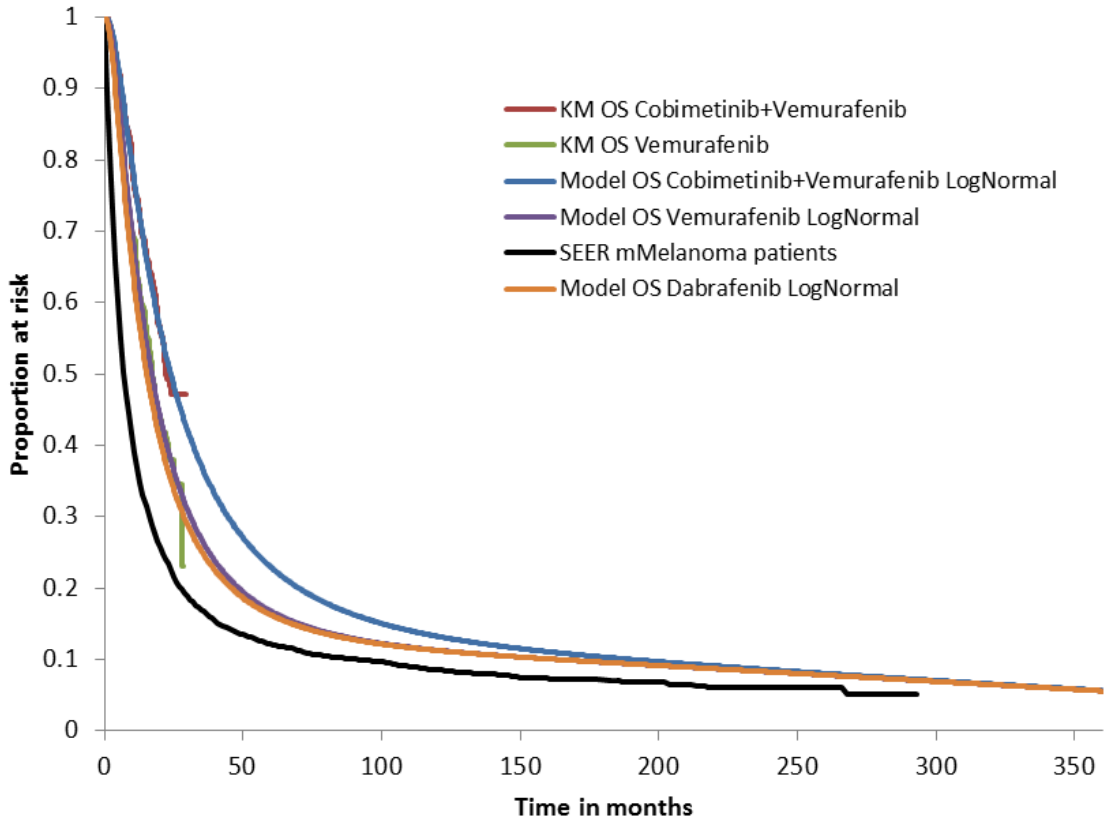


Figure 48 OS - Exponential

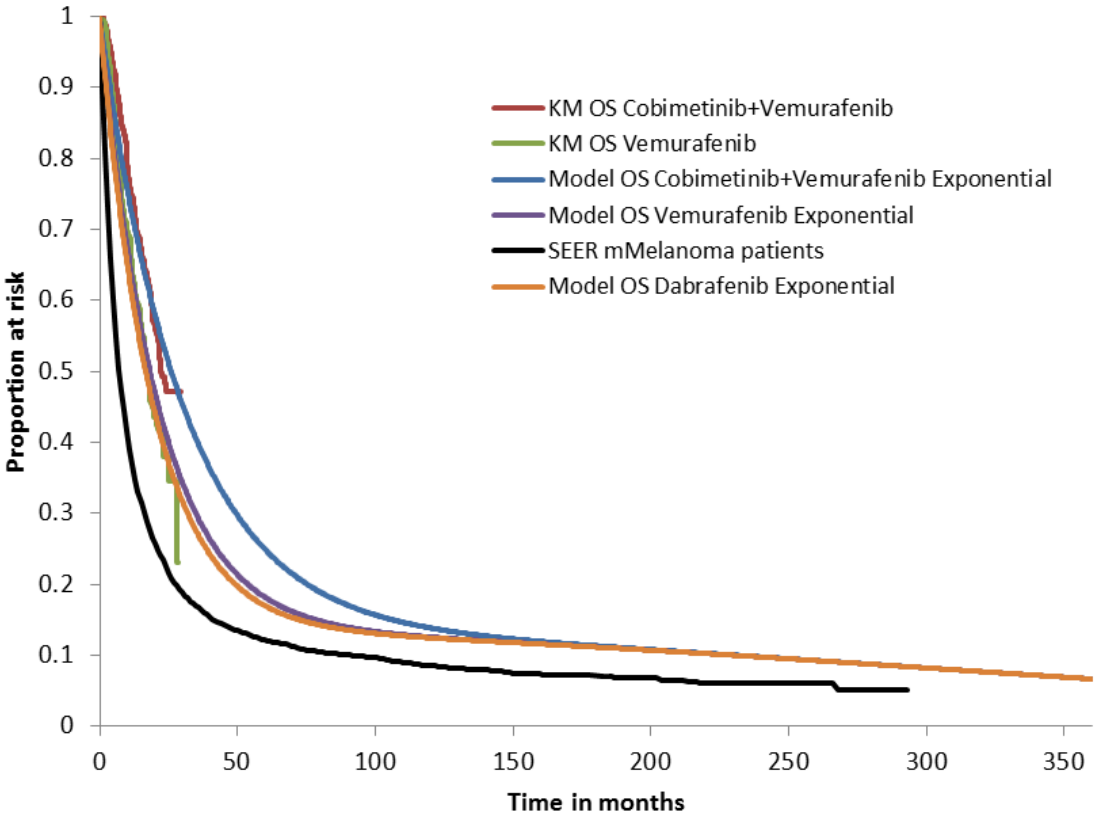


Figure 49 OS - Weibull

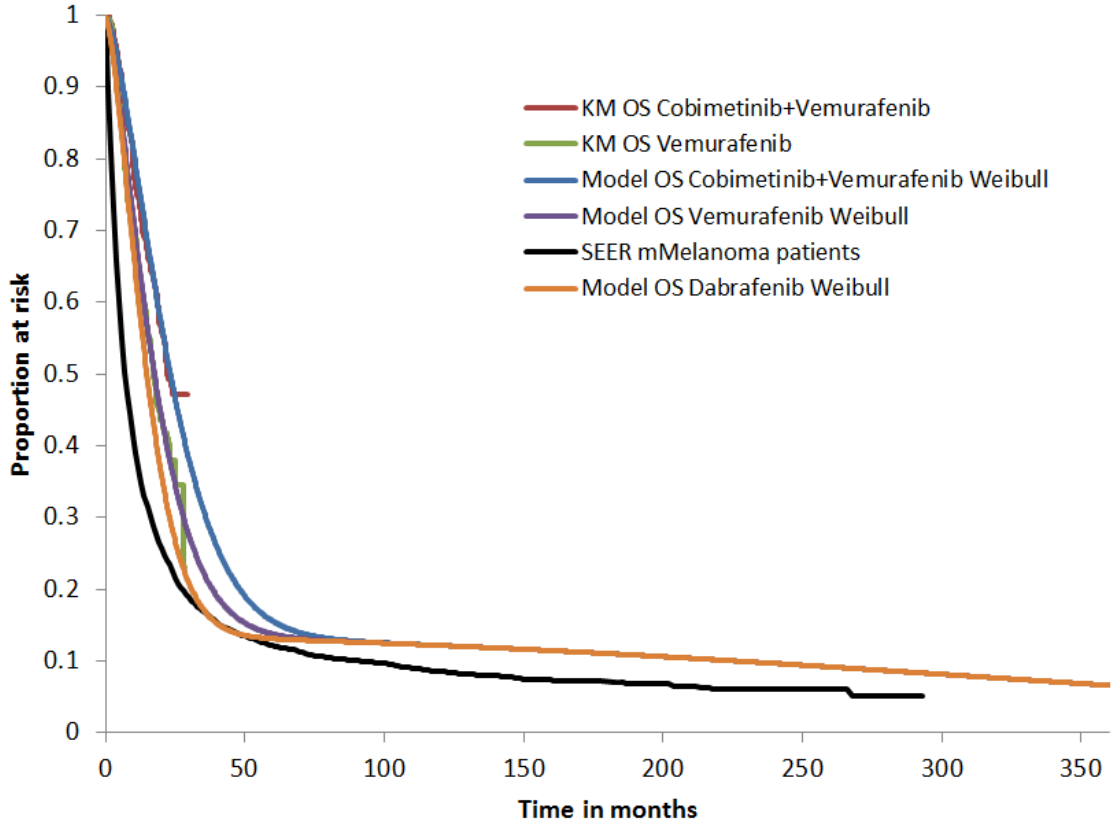


Figure 50 OS - Gamma

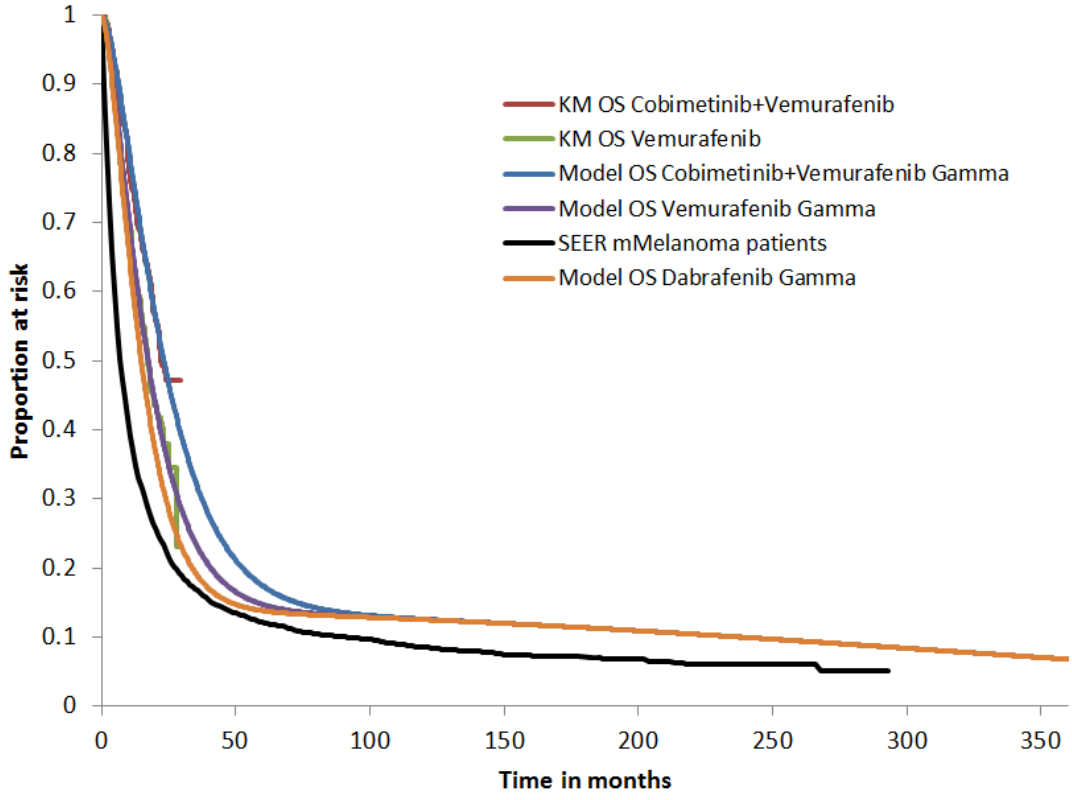


Figure 51 OS - LogLogistic

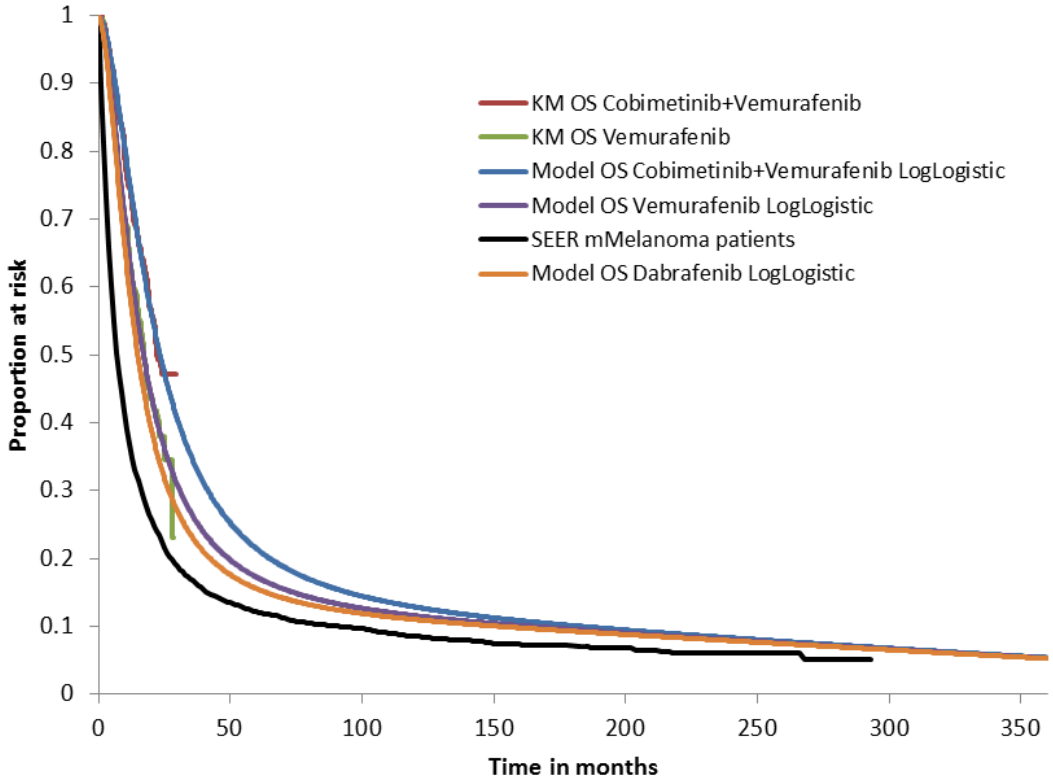
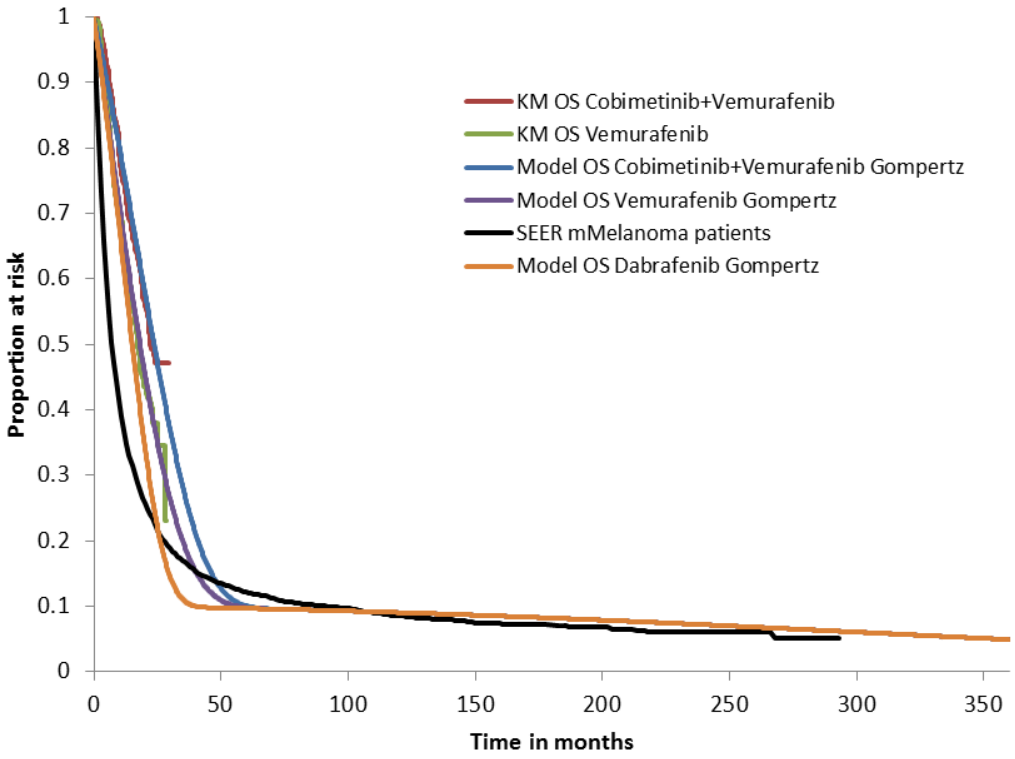


Figure 52 OS - Gompertz



Appendix 11: Search strategy for measurement and valuation of health effects

A systematic search was conducted 10th March 2015 and updated 9th December 2105. The following electronic data sources were searched for articles published up to 10 December 2015.

1. MEDLINE® In-process & Other Non-indexed Citations and OVID MEDLINE® 1946–present
2. Embase® 1974–present
3. Cochrane Library, comprising:
    a. Cochrane Database of Systematic Reviews (CDSR)
    b. Database of Abstracts of Reviews of Effects (DARE)
    c. Cochrane Central Register of Controlled Trials (CENTRAL)
    d. Cochrane Methodology Register (CMR)
    e. NHS Economic Evaluations Database (NHS EED)
    f. American College of Physicians (ACP) journal club
    g. Health technology Assessment (HTA)

Proceedings from the following congresses over the past 3 years (2013–2015) were interrogated for relevant abstracts:

1. International Society For Pharmacoeconomics and Outcomes Research (ISPOR) (US and European): http://www.ispor.org
2. American Society of Clinical Oncology (ASCO): http://www.asco.org/meetings
3. European Society for Medical Oncology (ESMO): http://www.esmo.org/
4. Society of Melanoma Research (SMR): http://www.societymelanomaresearch.org

Manufacturer submissions and evidence review group/assessment reports from NICE were reviewed for additional cost data:

1. NICE: https://www.nice.org.uk

The additional sources were also hand searched:

1. EQ-5D website: http://www.euroqol.org
2. Health Economics Research Centre database of mapping studies: http://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies
3. Reference lists of included studies

Table 85 Ovid MEDLINE ® In-Process & Other Non-Indexed Citations and Ovid MEDLINE ® 1946 to 10 March 2015 for HSUV studies

#	Searches	Results

#	Searches	Results
1	exp Melanoma/	77 265
2	melanoma$.mp.	102 432
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	22 962
4	or/1-3	119 311
5	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	4949
6	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	2539
7	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	6872
8	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	499
9	(15D or 16D or 17D).mp.	2106
10	("standard gamble" or SG).mp.	6797
11	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	1295
12	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	381
13	disutilit$.mp.	256
14	(health adj1 stat*).mp. or exp Health Status/	167 091
15	(utility adj1 (value* or weight*)).mp.	1027
16	exp statistical model/	292 979
17	preference$.mp.	110 874
18	*patient preference/	2165
19	(utilit* or "health utility index" or "utilities index").mp.	133 878
20	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1 014 174
21	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	739
22	quality of life index.mp. or exp "quality of life index"/	1231
23	quality adjusted life year.mp. or exp quality adjusted life year/	9108
24	(qaly or daly or "adjusted life").mp.	12 853

#	Searches	Results
25	("quality adjusted" or "disability adjusted").mp.	12 475
26	disability.mp. or exp disability/	162 160
27	disabled person.mp. or exp disabled person/	48 120
28	life expectancy.mp. or exp life expectancy/	29 540
29	(26 or 27) and 28	1405
30	(QoL or HRQoL or HRQL or "health related quality of life" or "health-related quality of life").mp.	44 830
31	quality of life.mp. or exp "quality of life"/	213 841
32	or/14-25,29	1 568 183
33	32 and (30 or 31)	54 401
34	or/5-13	23 675
35	33 or 34	71 463
36	4 and 35	341

Table 86 Cochrane search for HSUV studies, ran 10 March 2015

#	Searches	Results
1	exp Melanoma/	1058
2	melanoma$.mp.	2353
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	691
4	or/1-3	2846
5	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	2442
6	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	939
7	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	1130
8	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	169
9	(15D or 16D or 17D).mp.	124
10	("standard gamble" or SG).mp.	767
11	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	502

#	Searches	Results
12	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	307
13	disutilit$.mp.	204
14	(health adj1 stat*).mp. or exp Health Status/	11 965
15	(utility adj1 (value* or weight*)).mp.	1915
16	exp statistical model/	13 532
17	preference$.mp.	9423
18	*patient preference/	0
19	(utilit* or "health utility index" or "utilities index").mp.	11 062
20	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	36 459
21	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	45
22	quality of life index.mp. or exp "quality of life index"/	419
23	quality adjusted life year.mp. or exp quality adjusted life year/	4655
24	(qaly or daly or "adjusted life").mp.	6934
25	("quality adjusted" or "disability adjusted").mp.	6759
26	disability.mp. or exp disability/	13 595
27	disabled person.mp. or exp disabled person/	829
28	life expectancy.mp. or exp life expectancy/	2258
29	(26 or 27) and 28	166
30	(QoL or HRQoL or HRQL or "health related quality of life" or "health-related quality of life").mp.	11 016
31	quality of life.mp. or exp "quality of life"/	43 061
32	or/14-25,29	74 644
33	32 and (30 or 31)	14 171
34	or/5-13	5707
35	33 or 34	16 676
36	4 and 35	99

Table 87 HSUV study search: Embase 1974 to 10 March 2015

#	Searches	Results
1	exp Melanoma/	107 405
2	melanoma$.mp.	137 260
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	29 755
4	or/1-3	157 882
5	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	8699
6	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	5152
7	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	11 117
8	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	858
9	(15D or 16D or 17D).mp.	2829
10	("standard gamble" or SG).mp.	9192
11	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	1743
12	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	465
13	disutilit$.mp.	434
14	(health adj1 stat*).mp. or exp Health Status/	186 426
15	(utility adj1 (value* or weight*)).mp.	1750
16	exp statistical model/	115 515
17	preference$.mp.	130 288
18	*patient preference/	1797
19	(utilit* or "health utility index" or "utilities index").mp.	175 906
20	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1 100 519
21	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	1125
22	quality of life index.mp. or exp "quality of life index"/	3225
23	quality adjusted life year.mp. or exp quality adjusted life year/	14 837
24	(qaly or daly or "adjusted life").mp.	20 034

#	Searches	Results
25	("quality adjusted" or "disability adjusted").mp.	18 309
26	disability.mp. or exp disability/	204 242
27	disabled person.mp. or exp disabled person/	26 403
28	life expectancy.mp. or exp life expectancy/	43 782
29	(26 or 27) and 28	2301
30	(QoL or HRQoL or HRQL or "health related quality of life" or "health-related quality of life").mp.	70 253
31	quality of life.mp. or exp "quality of life"/	350 457
32	or/14-25,29	1 630 858
33	32 and (30 or 31)	76 594
34	or/5-13	37 174
35	33 or 34	103 014
36	4 and 35	670

Table 88 HSUV search update: Embase 9 December 2015

#	Searches	Results
1	exp Melanoma/	117 150
2	melanoma$.mp.	149 305
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	32 208
4	or/1-3	171 596
5	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	9900
6	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	5472
7	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	12 112
8	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	949
9	(15D or 16D or 17D).mp.	3014
10	("standard gamble" or SG).mp.	10 035

11	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	1881
12	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	483
13	disutilit$.mp.	499
14	(health adj1 stat*).mp. or exp Health Status/	200 459
15	(utility adj1 (value* or weight*)).mp.	1974
16	exp statistical model/	122 589
17	preference$.mp.	141 510
18	*patient preference/	2130
19	(utilit* or "health utility index" or "utilities index").mp.	190 511
20	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1 190 162
21	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	1209
22	quality of life index.mp. or exp "quality of life index"/	3405
23	quality adjusted life year.mp. or exp quality adjusted life year/	16 316
24	(qaly or daly or "adjusted life").mp.	22 066
25	("quality adjusted" or "disability adjusted").mp.	20 108
26	disability.mp. or exp disability/	224 031
27	disabled person.mp. or exp disabled person/	28 309
28	life expectancy.mp. or exp life expectancy/	47 152
29	(26 or 27) and 28	2484
30	(QoL or HRQoL or HRQL or "health related quality of life" or "health-related quality of life").mp.	76 896
31	quality of life.mp. or exp "quality of life"/	377 936
32	or/14-25,29	1 761 290
33	32 and (30 or 31)	83 572
34	or/5-13	40 683
35	33 or 34	112 466
36	4 and 35	741

37	limit 36 to yr="2015 -Current"	76

Table 89 Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE®: 1946 to present**:** ran 9 December 2015 – HSUV study search update

#	Searches	Results
1	exp Melanoma/	80 769
2	melanoma$.mp.	107 356
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	24 284
4	or/1-3	125 199
5	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	5513
6	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	2673
7	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	7319
8	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	558
9	(15D or 16D or 17D).mp.	2227
10	("standard gamble" or SG).mp.	7229
11	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	1383
12	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	401
13	disutilit$.mp.	282
14	(health adj1 stat*).mp. or exp Health Status/	176 315
15	(utility adj1 (value* or weight*)).mp.	1113
16	exp statistical model/	311 430
17	preference$.mp.	117 430
18	*patient preference/	2458
19	(utilit* or "health utility index" or "utilities index").mp.	143 059
20	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1 075 313
21	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or	778

	"mau").mp.	
22	quality of life index.mp. or exp "quality of life index"/	1304
23	quality adjusted life year.mp. or exp quality adjusted life year/	9837
24	(qaly or daly or "adjusted life").mp.	13 936
25	("quality adjusted" or "disability adjusted").mp.	13 518
26	disability.mp. or exp disability/	171 293
27	disabled person.mp. or exp disabled person/	50 888
28	life expectancy.mp. or exp life expectancy/	31 234
29	(26 or 27) and 28	1509
30	(QoL or HRQoL or HRQL or "health related quality of life" or "health-related quality of life").mp.	48 540
31	quality of life.mp. or exp "quality of life"/	229 148
32	or/14-25,29	1 661 521
33	32 and (30 or 31)	58 356
34	or/5-13	25 357
35	33 or 34	76 583
36	4 and 35	361
37	limit 36 to yr="2015 -Current"	27

Table 90 HSUV study search update: Cochrane Library: ran 9 December 2015

#	Searches	Results
1	exp Melanoma/	1077
2	melanoma$.mp.	2540
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	808
4	or/1-3	3115
5	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	2787
6	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	1098
7	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or	1251

	utility))).mp.	
8	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	187
9	(15D or 16D or 17D).mp.	141
10	("standard gamble" or SG).mp.	887
11	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	529
12	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	335
13	disutilit$.mp.	210
14	(health adj1 stat*).mp. or exp Health Status/	12 896
15	(utility adj1 (value* or weight*)).mp.	1958
16	exp statistical model/	13 652
17	preference$.mp.	10 561
18	*patient preference/	0
19	(utilit* or "health utility index" or "utilities index").mp.	12 110
20	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	40 745
21	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	50
22	quality of life index.mp. or exp "quality of life index"/	476
23	quality adjusted life year.mp. or exp quality adjusted life year/	4850
24	(qaly or daly or "adjusted life").mp.	7227
25	("quality adjusted" or "disability adjusted").mp.	7036
26	disability.mp. or exp disability/	15 319
27	disabled person.mp. or exp disabled person/	877
28	life expectancy.mp. or exp life expectancy/	2543
29	(26 or 27) and 28	182
30	(QoL or HRQoL or HRQL or "health related quality of life" or "health-related quality of life").mp.	12 755
31	quality of life.mp. or exp "quality of life"/	47 864
32	or/14-25,29	81 849

33	32 and (30 or 31)	15 264
34	or/5-13	6440
35	33 or 34	18 211
36	4 and 35	113
37	limit 36 to yr="2015 -Current" [Limit not valid in DARE; records were retained]	18

Figure 53 HSUV study search PRISMA flow diagram (original search)

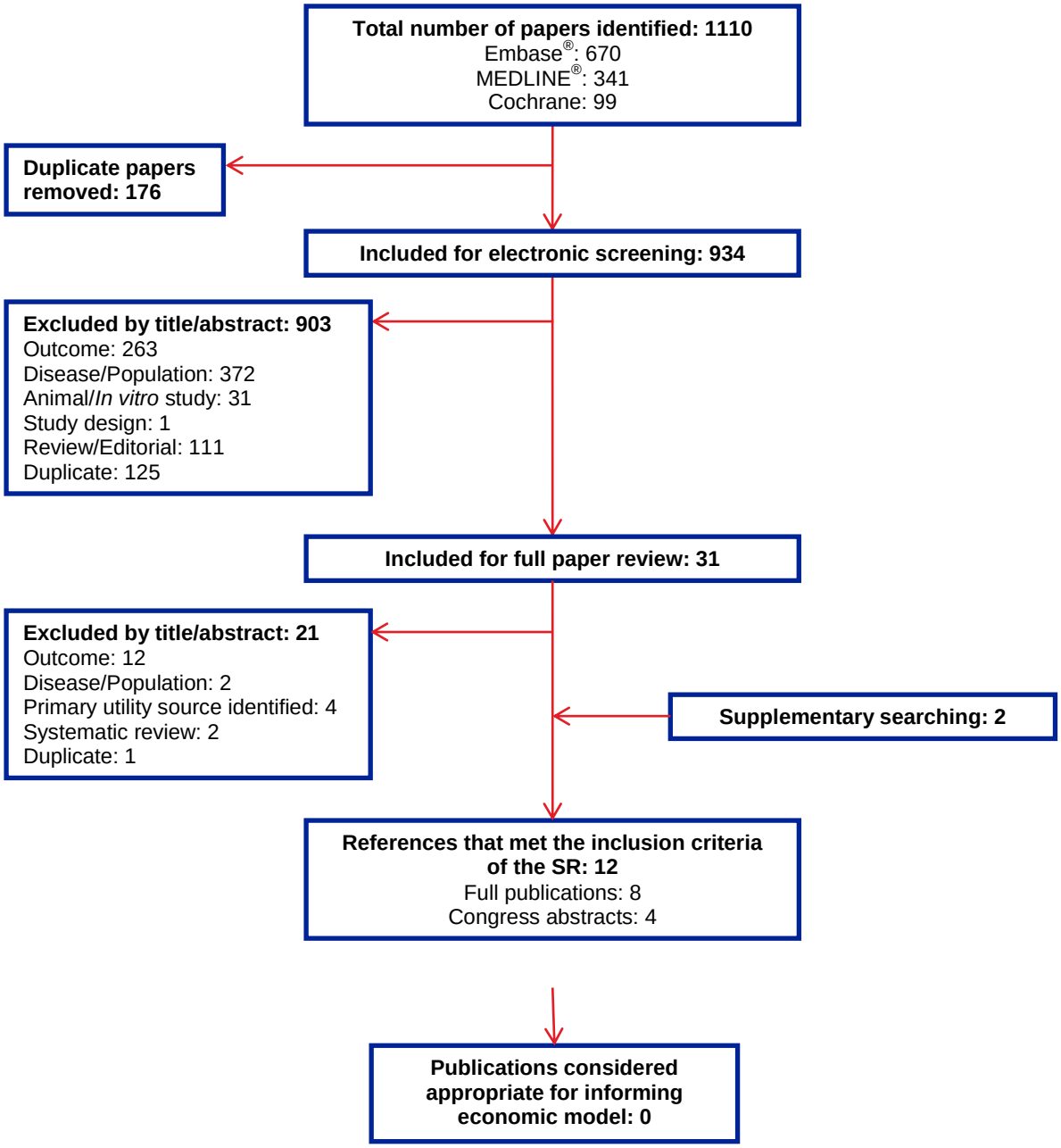
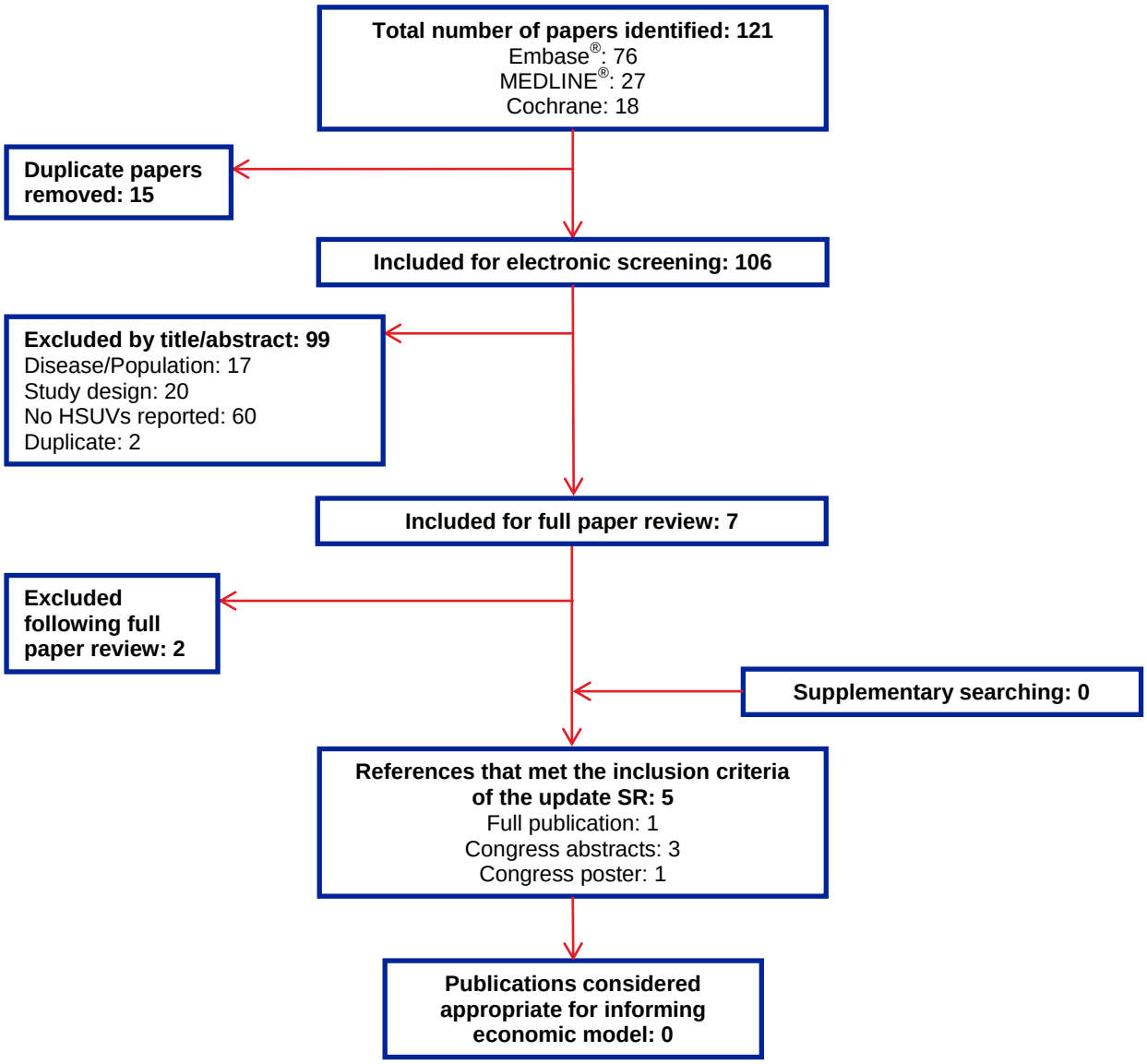


Figure 54 HSUV study search PRISMA flow diagram (update to search)



Appendix 12: Details of HSUV study results

Table 91 HSUV publications meeting inclusion criteria but not relevant to appraisal

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
Studies that were consistent with the NICE reference case but not considered appropriate to support the economic model (n = 2)				
Hatswell *et al*., 2014) USA [RCT multicentre]	Patients with unresectable malignant melanoma from the MDX010-20 trial (patients had received prior systemic therapy for advanced melanoma) N = 676	IPI vs IPI + gp100 vs gp100 • Pre-progression • Post-progression • Time-to-death < 1 year (179 days to death up to final month of life)	Derived using mapping algorithms to convert EORTC QLQ-C30 to EORTC-8D and SF-36 to SF-6D Mapping algorithms were not specific to patients with melanoma and mapped utilities have not been extracted	Although HSUVs were consistent with the NICE reference case in that patients described the health states using a validated instrument, and the valuation of the health states was based on UK societal values, the HSUVs were associated with the following limitations • HSUVs were derived by converting SF-36 and the EORTC QLQ-C30 scores to EQ-5D and SF-6D utilities; NICE guidance states a preference for EQ-5D-generated HSUVs • Relevance of HSUVs: post-progression and post-treatment HSUVs are specific to treatment with IPI only, IPI + gp100 and gp100 only
Paly *et al*., (2015) NR [RCT] (congress poster)	Treatment-naïve patients with advanced melanoma N = 288	NIVO vs DTIC • Baseline • During study treatment (every 6 weeks)	EQ-5D	Although HSUVs were consistent with the NICE reference case in that patients described the health states using a validated instrument, and the valuation of the health states was based on UK societal
		Baseline – NIVO	0.75 (0.23) [NR]	
		Baseline – DTIC	0.69 (0.32) [NR]	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
		Baseline – NIVO + DTIC	0.72 (NR) [NR]	values, the HSUVs were associated with the following limitations • Publication was available as a poster only and limited information was reported for population characteristics • Relevance of HSUVs: HSUVs were measured at baseline and post-treatment with NIVO and DTIC; treatment-specific HSUVs were not considered appropriate
		Mixed linear models of utility over time	Intercept, estimate (SE): 0.368 (0.034), $p < 0.0001$ Post-progression, estimate (SE): -0.074 (0.013), $p < 0.0001$ Days left: 29 or less estimate (SE): −0.022 (0.013), $p = 0.092$ Visit 1 EQ-5D, estimate (SE): 0.603 (0.040), $p < 0.0001$ Treatment: DTIC, estimate (SE): −0.069 (0.020), $p = 0.001$	
Studies that were not consistent with the NICE reference case for the incorporation of HRQoL into economic evaluations (n = 7)				
Beusterien *et al.*, (2009) UK, Australia, [observational study]	Utilities were derived from the general public in the UK and Australia (for	Non-intervention specific • Partial response • Stable disease • Progressive disease • Utility decrement for toxicity states	Vignettes valued using SG	HSUVs were not consistent with the NICE reference case • Health state descriptions were not provided by

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
	patients with advanced melanoma) N = 140	General public respondents: health state 1, partial response, all population	0.88 (NR) [0.01]	patients as per the NICE reference case; HSUVs were elicited from the general public via a direct valuation of health states vignettes using the SG approach
		General public respondents: health state 2, stable disease, UK population	0.77 (NR) [0.02]	
		General public respondents: health state 2, stable disease, all population	0.80 (NR) [0.01]	
		General public respondents: health state 3, progressive disease, UK population	0.59 (NR) [0.02]	
		General public respondents: health state 3, progressive disease, all population	0.52 (NR) [0.02]	
		General public respondents: health state 4, BSC, UK population	0.59 (NR) [0.02]	
		General public respondents: health state 4, BSC, all population	0.52 (NR) [0.02]	
		General public respondents: health state 5, utility decrement for toxicity states, hair loss (grade 1/2), UK population	−0.03 (NR) [0.01]	
		General public respondents: health state 5, utility decrement for toxicity states, hair loss (grade 1/2), all population	−0.03 (NR) [0.01]	
		General public respondents: health state 6, utility decrement for toxicity states, skin reaction (grade 1/2), UK population	−0.03 (NR) [0.01]	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
		General public respondents: health state 6, utility decrement for toxicity states, skin reaction (grade 1/2), all population	−0.06 (NR) [0.01]	
		General public respondents: health state 7, utility decrement for toxicity states, diarrhoea (grade 1/2), UK population	−0.06 (NR) [0.01]	
		General public respondents: health state 7, utility decrement for toxicity states, diarrhoea (grade 1/2), all population	−0.09 (NR) [0.01]	
		General public respondents: health state 8, utility decrement for toxicity states, nausea/vomiting (grade 1/2), UK population	−0.07 (NR) [0.01]	
		General public respondents: health state 8, utility decrement for toxicity states, nausea/vomiting (grade 1/2), all population	−0.10 (NR) [0.01]	
		General public respondents: health state 9, utility decrement for toxicity states; flu-like syndrome (grade 1/2), UK population	−0.09 (NR) [0.01]	
		General public respondents: health state 9, utility decrement for toxicity states, flu-like syndrome (grade 1/2), all population	−0.11 (NR) [0.01]	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
		General public respondents: health state 10, utility decrement for toxicity states, stomatitis (grade 1/2), UK population	−0.10 (NR) [0.02]	
		General public respondents: health state 10, utility decrement for toxicity states, stomatitis (grade 1/2), all population	−0.13 (NR) [0.01]	
		General public respondents: health state 11, utility decrement for toxicity states, symptomatic melanoma, UK population	−0.11 (NR) [0.02]	
		General public respondents: health state 11, utility decrement for toxicity states, symptomatic melanoma. all population	−0.16 (NR) (0.01)	
		General public respondents: health state 12, utility decrement for toxicity states, 1-day in-/outpatient stay for severe toxicity (grade 3/4), UK population	−0.11 (NR) [0.02]	
		General public respondents: health state 12, utility decrement for toxicity states, 1-day in-/outpatient stay for severe toxicity (grade 3/4), all population	−0.13 (NR) [0.01]	
		General public respondents: health state 13, utility decrement for toxicity states, 2–5-day hospitalisation for severe toxicity (grade 3/4), UK population	−0.13 (NR) [0.02]	
		General public respondents: health state	−0.17 (NR) [0.01]	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
		13, utility decrement for toxicity states, 2–5-day hospitalisation for severe toxicity (grade 3/4), all population		
Hogg *et al*., (2010) Canada [observational study]	Utilities were derived from general public respondents in Canada (for patients with advanced melanoma) N = 87	Non-intervention specific • Partial disease • Stable disease • Progressive disease • Utility decrement for toxicity states and hospitalisation	Vignettes valued using SG	HSUVs were not consistent with the NICE reference case • Health state descriptions were not provided by patients as per the NICE reference case; HSUVs were elicited from the general public via a direct valuation of health state vignettes (validated using clinical experts) using the SG approach
		General public respondents: health state 1, partial response, Canadian population	0.84 (NR) [0.02]	
		General public respondents: health state 2, stable disease, Canadian population	0.79 (NR) [0.02]	
		General public respondents: health state 3, progressive disease, Canadian population	0.55 (NR) [0.02]	
		General public respondents: health state 4, BSC, Canadian population	0.54 (NR) [0.02]	
		General public respondents: health state 5, toxicity state, skin reaction (utility decrement), Canadian population	−0.04 (NR) [0.01]	
		General public respondents: health state 6, toxicity state, hair loss (utility decrements), Canadian population	−0.05 (NR) [0.01]	
		General public respondents: health state 7, toxicity state, diarrhoea (utility decrement), Canadian population	−0.06 (NR) [0.01]	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
		General public respondents: health state 8, toxicity state, nausea/vomiting (utility decrement), Canadian population	−0.07 (NR) [0.01]	
		General public respondents: health state 9, toxicity state, flu-like syndrome (utility decrement), Canadian population	−0.08 (NR) [0.01]	
		General public respondents: health state 10, toxicity state, stomatitis (utility decrement), Canadian population	−0.09 (NR) [0.01]	
		General public respondents: health state 11, toxicity state , 1 day out/inpatient care for grade 3/4 toxicity (utility decrement), Canadian population	−0.11 (NR) [0.01]	
		General public respondents: health state 12, hospitalisation for grade 3/4 toxicity (utility decrement), Canadian population	−0.15 (NR) [0.01]	
Coleman King *et al.*, (2011) USA [observational study]	Utilities were derived from patients with melanoma, all stages (1–4) N = 163	Non-intervention specific • Newly diagnosed • Established diagnosis • Overall stage for melanoma (stages 1–4)	TTO	HSUVs were not consistent with the NICE reference case • The valuation of the health states was not based on UK societal preferences and the description of the health states was not elicited from patients; pre-defined health state descriptions were valued by
		Patients with melanoma: new diagnosis, stage 3, TTO	0.534 (0.291) [NR]	
		Patients with melanoma: new diagnosis, stage 4	0.693 (0.329) [NR]	
		Patients with melanoma: established diagnosis, stage 3	0.908 (0.123) [NR]	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
		Patients with melanoma: established diagnosis, stage 4	0.527 (0.339) [NR]	patients using the TTO approach • Previous treatment detail not reported
		Patients with melanoma: overall, stage 3	0.720 (0.282) [NR]	
Askew *et al*., (2011) USA [observational study]	Patients with melanoma (AJCC all stage) N = 273	Mapping algorithm to convert FACT-M scores to EQ-5D utilities (reports HSUVs for follow up surveillance, on treatment and stage 3/4 melanoma)	Reports original mapping algorithm: EQ-5D = 0.0037*FACT-M + 0.2238, $R^{2:}$ 0.499 (specific to patients with melanoma)	• Reports a mapping algorithm for converting FACT-M scores to EQ-5D utilities • Previous treatment detail not reported
Curl *et al*., (2014) USA [CUA]	Utilities for patients with advanced melanoma obtained from clinical experts N = NR	IPI (2nd-line therapy to vemurafenib) specific • Post-treatment • Post-progression	Clinical experts (no further detail reported)	HSUVs were not consistent with the NICE reference case • Health state descriptions were not provided by patients as per the NICE reference case; health states were described by clinical experts
		Patients with melanoma: 3rd-line salvage (for patients who switched treatments at first time progression, had a 2nd-line IPI treatment which led to no disease control leading to 3rd-line salvage)	0.46 (NR) [NR]	
Tromme *et al.*, (2014) Belgium [observational study]	Patients with melanoma (all stages) N = 395	• Treatment (intervention detail not reported • Remission • Disutilities	EQ-5D-3L	HSUVs were not consistent with the NICE reference case • The valuation of the health states (EQ-5D-5L) was not based on UK societal preferences; the Netherlands societal valuations were used
		Patients with advanced melanoma: stage III-treatment, from months 1–3 of the beginning of the treatment	0.535 (0.278) [0.072] {0.395–0.676}	
		Patients with advanced melanoma: stage III-remission, from month 4 of the beginning of the treatment	0.703 (0.156) [0.022] {0.659–0.746}	
		Patients with advanced melanoma: stage IV-treatment, from start of the treatment	0.583 (0.192) [0.030] {0.524–0.642}	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
		Patients with advanced melanoma: stage IV-remission, from start of remission	0.796 (0.167) [0.045] {0.708–0.883}	
		Patients with advanced melanoma: stage III-treatment, disability weights, months 1–3 from the beginning of the treatment	0.372 (0.268) [0.069] {0.236–0.508}	
		Patients with advanced melanoma: stage III-remission, disability weights, from month 4 of the beginning of the treatment	0.207 (0.147) [0.021] {0.166–0.247}	
		Patients with advanced melanoma: stage IV-treatment, disability weights, from the start of the treatment	0.315 (0.188) [0.029] {0.258–0.373}	
		Patients with advanced melanoma: stage IV-remission, disability weights, from the start of remission	0.136 (0.122) [0.033] {0.072–0.200}	
Harrison and Kim, (2015) Australia, [RCT]	Patients with unresectable or metastatic stage III/IV melanoma N = 409	NIVO vs DTIC • Baseline • Pre-progression • Post-progression	EQ-5D 3L	HSUVs were not consistent with the NICE reference case • The valuation of the health states was not based on UK societal preferences; Australian societal valuations were used • Information was available in abstract only, and limited information was reported for
		Baseline – NIVO	0.78 (NR) [NR] {0.75–0.81}	
		Baseline – DTIC	0.71 (NR) [NR] {0.67–0.75}	
		Pre-progression – NIVO	0.84 (NR) [NR] {0.83–0.85}	
		Pre-progression – DTIC	0.78 (NR) [NR] {0.76–0.81}	
		Post-progression – NIVO	0.83 (NR) [NR] {0.80–0.86}	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
		Post-progression – DTIC	0.70 (NR) [NR] {0.66–0.74}	population characteristics • Relevance of HSUVs: post-progression HSUVs are specific to treatment with NIVO and DTIC
Studies with insufficient information to determine if utilities are consistent with the NICE reference case (n = 8)				
Batty *et al.*, (2011) UK [RCT (multicentre)]	Patients with unresectable malignant melanoma from the MDX010-20 RCT N = NR	IPI + gp100 vs IPI vs gp100 • Baseline • Pre-progression • Post-progression	SG vignettes and mapping algorithm-generated HSUVs (EORTC QLQ-C30 to EORTC-8D, SF-36 to SF-6D)	It is unclear whether the HSUVs generated using two of the three utility methods described in the study, the EORTC-6D and the SF-6D, were consistent with the NICE reference case, as the valuation of the health states was not reported (the third method, vignettes, are not consistent with the NICE reference case). In addition, HSUVs were based on the following limitations • HSUVs were derived using the SF-6D (mapped from SF-36), EORTC-6D (mapped from EORTC QLQ-C30) and vignettes; NICE have stated a preference for utility data derived using the EQ-5D instrument • Progression HSUVs relate to patients who received treatment with IPI + gp100 vaccine, IPI + placebo, or gp100 vaccine alone from the MDX010-20 RCT
		Patients with advanced melanoma: progression free health state, SG vignettes	0.77 (NR) [NR]	
		Patients with advanced melanoma: progression free health state, SF-6D	0.64 (NR) [NR]	
		Patients with advanced melanoma: progression free health state, EORTC-8D	0.8 (NR) [NR]	
		Patients with advanced melanoma: post-progression state, SG vignettes	−0.18 (NR) [NR]	
		Patients with advanced melanoma: post-progression state, SF-6D	−0.02 (NR) [NR]	
		Patients with advanced melanoma: post-progression state, EORTC-8D	−0.04 (NR) [NR]	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
Batty *et al.*, 2012) UK [RCT (multicentre)]	Patients with unresectable malignant melanoma from the MDX010-20 RCT N = NR	IPI + gp100 vs IPI vs gp100 • Baseline • Progression • Time-to-death	SF-6D, EORTC-8D and vignette-generated utilities (study did not report use of mapping)	It is unclear whether the HSUVs generated using two of the three utility methods described in the study (the EORTC-6D and the SF-6D) were consistent with the NICE reference case, as the valuation of the health states was not reported (the third method, vignettes, are not consistent with the NICE reference case). In addition, HSUVs were based on the following limitations • HSUVs were derived using the SF-6D (mapped from SF-36), EORTC-6D (mapped from EORTC QLQ-C30) and vignettes; NICE have stated a preference for utility data derived using the EQ-5D instrument • Relevance of HSUVs: post-progression HSUVs are specific to treatment with IPI + gp100 vaccine, IPI + placebo, or gp100 vaccine alone
		Patients with advanced melanoma: baseline , vignette-generated utilities	0.77 (NR) [NR]	
		Patients with advanced melanoma: baseline, SF-6D	0.64 (NR) [NR]	
		Patients with advanced melanoma: baseline, EORTC-8D	0.801 (NR) [NR]	
		Patients with advanced melanoma: disease progression, vignette-generated utilities	0.59 (NR) [NR]	
		Patients with advanced melanoma: disease progression, SF-6D	0.619 (NR) [NR]	
		Patients with advanced melanoma: disease progression, EORTC-8D	0.763 (NR) [NR]	
		Patients with advanced melanoma: baseline, time-to-death, SF-6D	0.826 (NR) [NR]	
		Patients with advanced melanoma: baseline, time-to-death, EORTC-8D	0.655 (NR) [NR]	
		Patients with advanced melanoma: time-to-death (180 days prior to death), SF-6D	0.628 (NR) [NR]	
		Patients with advanced melanoma: time-to-death (180 days prior to death), EORTC-8D	0.505 (NR) [NR]	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
Beusterien *et al.*, (2003) USA [RCT (multicentre)]	Patients with melanoma (stages NR) N = 305 (randomised) N = 301 (ITT)	Histamine dihydrochloride plus IL-2 vs IL-2 only • Baseline • Post-treatment • 1 year post-diagnosis • 1–5 years post-diagnosis • > 5 years post-diagnosis • 1 year post-treatment (NR)	QWB	It is unclear whether the HSUVs generated were consistent with the NICE reference case as the valuation of the health states was not reported. In addition, HSUVs were based on the following limitations • HSUVs in this study were derived using the QWB instrument; NICE guidance states a preference for EQ-5D-generated HSUVs • Relevance of HSUVs: post-treatment utilities are specific to histamine dihydrochloride plus IL-2, or IL-2 only
		Patients with metastatic melanoma: baseline, ITT overall melanoma population, IL-2 alone	0.6 (NR) [NR]	
		Patients with metastatic melanoma: baseline, ITT overall melanoma population, IL-2 + histamine	0.6 (NR) [NR]	
		Patients with metastatic melanoma: baseline, ITT liver metastases population, IL-2 alone	0.6 (NR) [NR]	
		Patients with metastatic melanoma: baseline, ITT liver metastases population, IL-2 + histamine	0.6 (NR) [NR]	
		Patients with metastatic melanoma: cycle 2, ITT overall melanoma population, IL-2 alone (difference from baseline between IL-2 alone and histamine + IL-2)	0.06 (NR) [NR]	
		Patients with metastatic melanoma: cycle 2, ITT overall melanoma population, IL-2 + histamine (difference between IL-2 alone and histamine + IL-2)	0.06 (NR) [NR]	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
		Patients with metastatic melanoma: cycle 3, ITT overall melanoma population, IL-2 alone, (difference between IL-2 alone and histamine + IL-2)	0.09 (NR) [NR]	
		Patients with metastatic melanoma: cycle 3, ITT overall melanoma population, IL-2 + histamine (difference between IL-2 alone and histamine + IL-2)	0.09 (NR) [NR]	
		Patients with metastatic melanoma: cycle 4, ITT overall melanoma population, IL-2 alone (difference between IL-2 alone and histamine + IL-2)	0.07 (NR) [NR]	
		Patients with metastatic melanoma: cycle 4, ITT overall melanoma population, IL-2 alone (difference between IL-2 alone and histamine + IL-2)	0.07 (NR) [NR]	
		Patients with metastatic melanoma: cycle 5, ITT overall melanoma population, IL-2 alone (difference between IL-2 alone and histamine + IL-2)	0.06 (NR) [NR]	
		Patients with metastatic melanoma: cycle 5, ITT overall melanoma population, IL-2 alone (difference between IL-2 alone and histamine + IL-2)	0.06 (NR) [NR]	
Ko *et al.*, (2003) [observational	Patients with melanoma (stages NR)	• 1 and 5 year post-diagnosis • Post-treatment	HALeX	It is unclear whether the HSUVs generated were consistent with

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
study]	N = 92	Patients with melanoma: acute period (1 year after diagnosis)	0.73 (0.29) [NR]	the NICE reference case, as the valuation of the health states was not reported. In addition, HSUVs were based on the following limitations • HSUVs in this study were derived using the HALeX and most likely valued using US societal valuations (US study, valuation reference not reported) (UK preferences would be preferred); NICE have stated a preference for utility data derived using the EQ-5D instrument
		Patients with melanoma: short-term period (1–5 years)	0.75 (0.24) [NR]	
		Patients with melanoma: long-term period (5 years)	0.78 (0.23) [NR]	
		Patients with melanoma: 1 year after treatment (no further information reported)	0.73 (NR) [NR]	
Long *et al.*, (2015) NR, [RCT]	Treatment-naïve patients with advanced melanoma N = 418	NIVO vs DTIC • Baseline • During study treatment (every 6 weeks)	EQ-5D (type not reported)	It is unclear whether the HSUVs generated were consistent with the NICE reference case, as the valuation of the health states was not reported. In addition, HSUVs were based on the following limitations • Relevance of HSUVs: HSUVs were measured at baseline and post-treatment with NIVO and DTIC; treatment-specific HSUVs were not considered appropriate
		Baseline – NIVO (EQ-5D)	0.778 (NR) [NR] (Oster *et al.*)	
		Baseline – DTIC (EQ-5D)	0.711 (NR) [NR] (Oster *et al.*)	
		Improvements from baseline to drop out – NIVO	Improvements from week 7 (0.027; $p = 0.011$) through week 49 (0.045; $p = 0.034$)	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
		Improvements from baseline to drop out – DTIC	No change from baseline	
Grob *et al*., (2015) NR, [RCT]	Patients with previously untreated *BRAF* Val600Glu or Val600Lys mutant unresectable or metastatic melanoma N = 704	DTIC + trametinib or vemurafenib • During study treatment (week 8, 16, 24, 32, 40, 48) • Disease progression	EQ-5D 3L	It is unclear whether the HSUVs generated were consistent with the NICE reference case, as the valuation tariff of the health states was not reported. In addition, HSUVs were based on the following limitations • Relevance of HSUVs: HSUVs are specific to treatment with DTIC + trametinib or vemurafenib (EQ-5D RCT data available)
		Combination therapy	0·751 (NR) [NR]	
		Vemurafenib	0·715 (NR) [NR]	
		Changes to utility:		
		Post-treatment, week 8, DTIC + trametinib, vemurafenib, respectively	0·08, −0.01	
		Post-treatment, week 16, DTIC + trametinib, vemurafenib, respectively	0.08, 0.00	
		Post-treatment, week 24, DTIC + trametinib, vemurafenib, respectively	0.07, −0.02	
		Post-treatment, week 32, DTIC + trametinib, vemurafenib, respectively	0.06, −0.05	
		Post-treatment, week 40, DTIC + trametinib, vemurafenib, respectively	0.07, −0.04	
		Post-treatment, week 48, DTIC + trametinib, vemurafenib, respectively	0.07, −0.04	
		Disease progression, DTIC + trametinib, vemurafenib, respectively	0.07, −0.05	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
Abernethy *et al*., (2015) NR, [RCT]	Treatment-naïve patients with advanced melanoma from an RCT (CheckMate 069), further detail not reported N = 142	IPI vs NIVO + IPI • Baseline • During study treatment, week 7 and 13	EQ-5D (type not reported)	It is unclear whether the HSUVs generated were consistent with the NICE reference case as the valuation tariff of the health states was not reported. In addition, HSUVs were based on the following limitations • Publication was available as a congress abstract only, and limited patient and utility data was reported • Relevance of HSUVs: post-treatment HSUVs are specific to treatment with NIVO and IPI, or IPI alone
		Baseline – IPI	0.847 (NR) [NR]	
		Baseline – NIVO	0.861 (NR) [NR]	
		Week 7 – IPI	0.789 (NR) [NR]	
		Week 7 – NIVO	0.788 (NR) [NR]	
		Week 13 – IPI	0.834 (NR) (NR)	
		Week 13 – NIVO	0.894 (NR) [NR]	

Reference, year, country [study design]	Population	Utility data	Utility instrument, mean HSUV (or disutility) (SD),[SE], {95% CI}	Rationale for exclusion
Porter *et al*., (2014) UK, [RCT (multicentre)] (congress abstract)	Patients with unresectable malignant melanoma (CA184-024 trial) (previously untreated) N = NR	IPI vs placebo • Time-to-death > 1 year (post-treatment) • Final month of life (post-treatment) • AEs	EORTC QLQ-C30 mapped to EORTC-8D Reference for mapping algorithm not reported, mapped utilities not extracted	It is unclear whether the HSUVs generated were consistent with the NICE reference case, as the valuation of the health states was not reported. In addition, HSUVs were based on the following limitations • HSUVs were derived from EORTC QLQ-C30 scores mapped to EORTC-8D; NICE guidance states a preference for EQ-5D utility data (EQ-5D RCT data available) • Publication was available as a congress abstract only, and limited patient and utility data was reported • Relevance of HSUVs: post-treatment HSUVs are specific to treatment with IPI or placebo

Appendix 13: Details of cost and resource use literature search

The following electronic data sources were searched for articles published between 1 January 2000 and 9 December 2015 (no start date to 10 December 2015 for EconLit):

4. MEDLINE® In-Process & Other Non-indexed Citations and OVID MEDLINE1946–present
5. Embase® 1974–present
6. Cochrane Library, comprising:
    a. Cochrane Database of Systematic Reviews (CDSR)
    b. Database of Abstracts of Reviews of Effects (DARE)
    c. Cochrane Central Register of Controlled Trials (CENTRAL)
    d. Cochrane Methodology Register (CMR)
    e. NHS Economic Evaluations Database (NHS EED)
    f. American College of Physicians (ACP) journal club
    g. Health technology Assessment (HTA)
7. EconLit 1886–present

Proceedings from the following congresses over the past 3 years (2013–2015) were interrogated for relevant abstracts:

5. International Society For Pharmacoeconomics and Outcomes Research (ISPOR) (US and European): http://www.ispor.org
6. American Society of Clinical Oncology (ASCO): http://www.asco.org/meetings
7. European Society for Medical Oncology (ESMO): http://www.esmo.org/
8. Society of Melanoma Research (SMR): http://www.societymelanomaresearch.org

Manufacturer submissions and evidence review group/assessment reports from NICE were reviewed for additional cost data:

2. NICE: https://www.nice.org.uk

The additional sources were also hand searched:

4. Research Papers in Economics (RePEc): http://repec.org/docs/RePEcIntro.html
5. Reference lists of included studies

Table 92 Cost and resource use search string: Embase®, ran 9 December 2015

#	Searches	Results
1	exp Melanoma/	117 150
2	melanoma$.mp.	149 305
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	32 208
4	or/1-3	171 596
5	(Advanced or unresectable or metastatic or BRAF V600).mp.	639 505
6	Cost$.mp.	761 517
7	(Resource adj2 (utili$ation or use$)).mp.	10 866
8	Cost of illness/	16 105
9	Cost control/	54 177
10	Financial management/	105 592
11	Health care cost/	145 294
12	Health care utilization/	46 996
13	Health care financing/	11 912
14	Health economics/	35 010
15	Hospital cost/	15 617
16	(fiscal or financial or finance or funding).tw.	123 711
17	(cost adj estimate$).mp.	2341
18	(cost adj variable$).mp.	177
19	(unit adj cost$).mp.	2986
20	or/6-19	974 748
21	4 and 5 and 20	965
22	(animals not (humans and animals)).mp.	628 878
23	21 not 22	954
24	limit 23 to yr="2000 -Current"	868

Table 93 Cost and resource use search string: MEDLINE® and MEDLINE® In-Process, ran 9 December 2015

#	Searches	Results
1	exp Melanoma/	80 769
2	melanoma$.mp.	107 356
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	24 284
4	or/1-3	125 199
5	(Advanced or unresectable or metastatic or BRAF V600).mp.	450 716
6	Cost$.mp.	503 292
7	(Resource adj2 (utili$ation or use$)).mp.	7722
8	Cost of illness/	20 329
9	Cost control/	20 855

10	Financial management/	15 661
11	Health care costs/	30 491
12	"Patient Acceptance of Health Care"/	34 292
13	Health care financing.mp.	2254
14	Economics, Medical/	9054
15	Hospital costs/	8635
16	(fiscal or financial or finance or funding).tw.	98 180
17	(cost adj estimate$).mp.	1625
18	(cost adj variable$).mp.	123
19	(unit adj cost$).mp.	1796
20	or/6-19	628 668
21	4 and 5 and 20	400
22	(animals not (humans and animals)).mp.	4 050 526
23	21 not 22	378
24	limit 23 to yr="2000 -Current"	319

Table 94 Cost and resource use search string: Cochrane, ran 9 December 2015

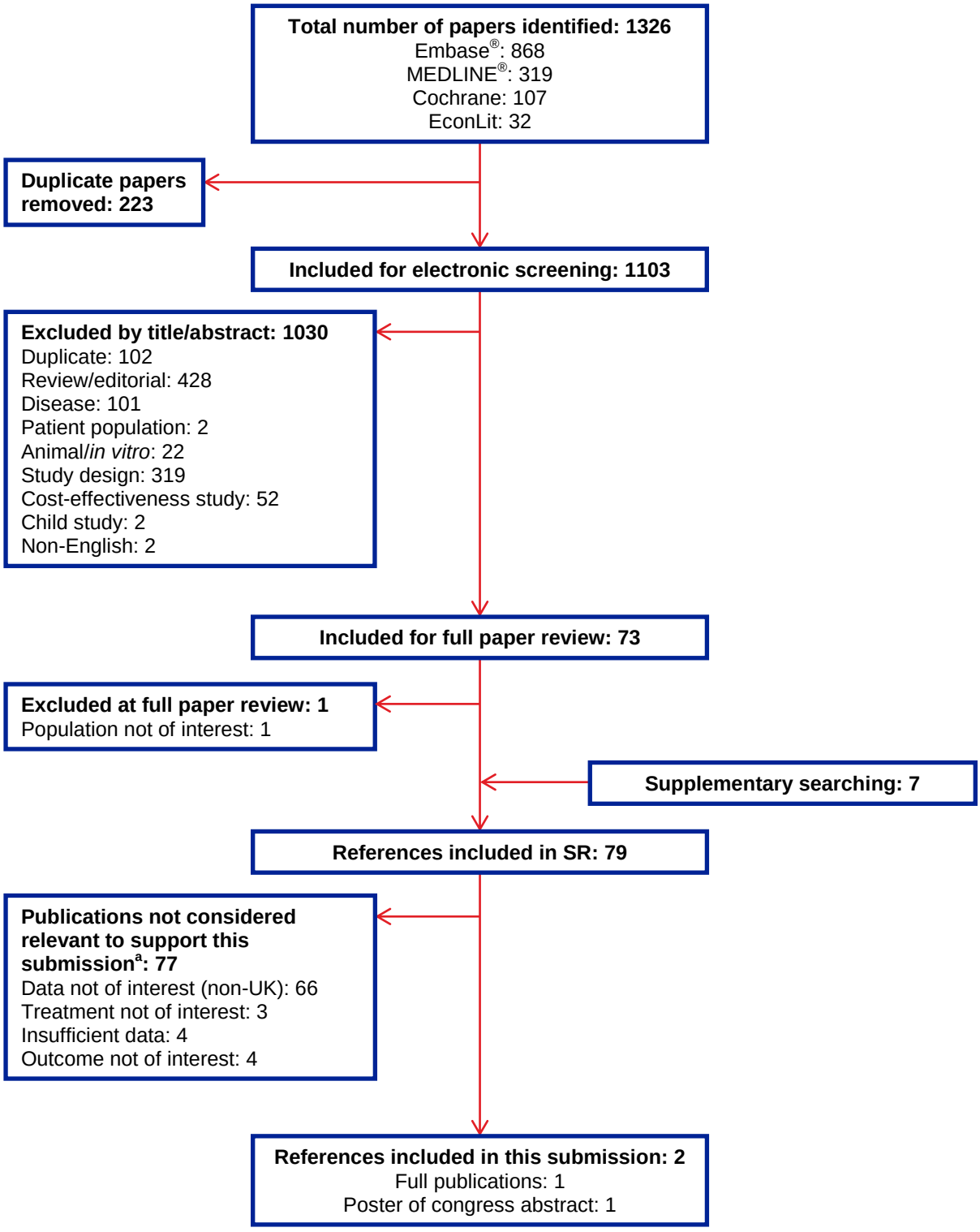
#	Searches	Results
1	exp Melanoma/	1077
2	melanoma$.mp.	2540
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	808
4	or/1-3	3115
5	(Advanced or unresectable or metastatic or BRAF V600).mp.	34 437
6	Cost$.mp.	62 727
7	(Resource adj2 (utili$ation or use$)).mp.	5987
8	Cost of illness/	1144
9	Cost control/	274
10	Financial management/	13
11	Health care costs/	4189
12	"Patient Acceptance of Health Care"/	1957
13	Health care financing.mp.	131
14	Economics, Medical/	36
15	Hospital costs/	1395
16	(fiscal or financial or finance or funding).tw.	32 413
17	(cost adj estimate$).mp.	2388
18	(cost adj variable$).mp.	87
19	(unit adj cost$).mp.	5158
20	or/6-19	74 437
21	4 and 5 and 20	122

22	(animals not (humans and animals)).mp.	1516
23	21 not 22	120
24	limit 23 to yr="2000 -Current" [Limit not valid in DARE; records were retained]	107

Table 95 Cost and resource use search string: EconLit®, ran 10 December 2015

#	Searches	Results
1	melanoma$.mp.	13
2	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.	22
3	1 or 2	32

Figure 55 Cost and resource use literature search PRISMA flow diagram



Appendix 14: [redacted]

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Single technology appraisal

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

Dear Denzyl,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 5th February 2016 from Roche Products. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on 15th March 2016. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted]. Any procedural questions should be addressed to [redacted]

Yours sincerely

Joanna Richardson
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. Please provide a breakdown of reasons for patients' withdrawal for both treatment arms, as well as the reason for the physician's decision to withdraw patients in the vemurafenib + cobimetinib treatment arm of the coBRIM trial (Table 13, page 59).

A2. The clinical study report (CSR) (section 3.10.8) states that sensitivity analyses were conducted for progression free survival (PFS) (3 analyses) and overall survival (OS) (2 analyses) but in the company submission (CS) (page 54) only the PFS sensitivity analyses are mentioned, not the OS ones. The CS states that the sensitivity analyses had no impact on results for PFS, but since the OS sensitivity analyses are not mentioned it's not clear whether these affected results or not. Please could you provide the results of these analyses, or provide a statement regarding the results of the OS sensitivity analyses.

A3. The CSR (section 3.10.16.2) states that a sensitivity analysis of PFS censored for missing visits was not performed as the number of patients with missing visits was very low. However, the CS (page 54) implies this sensitivity analysis was performed and showed no impact on the results from the primary analysis. Please explain this discrepancy.

A4. In section 4.10.4 of the CS (Indirect and mixed treatment comparisons), it is stated that 29 unique trials were identified from 35 publications. The PRISMA flowchart in Appendix 4 (Figure 35) shows that there were 33 publications of 25 unique RCTs. Please clarify this discrepancy in figures for publications and trials. Please supply a list of references for all of the publications included in the NMA, highlighting those references that were included in the 'restricted network' of BRAF mutation positive studies.

A5. **Priority question.** In section 4.10.12 of the CS it is stated that "Evidence from a previously conducted NMA (Bexelius 2014) found the accelerated failure time (AFT) survival model was a better fit compared with the proportional hazards (PH) model, for trials in metastatic melanoma" There is no entry in the reference list for Bexelius 2014 and no full publication has been provided. Please can you supply the citation and the full text.

A6. **Priority question**. In section 4.10.12 of the CS the main assumption for the NMA is stated to be that the treatment node of dacarbazine or paclitaxel in the Flaherty trial is considered to interact in the same way as dacarbazine in other trials. Please state

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the justification for this assumption, and provide a sensitivity analysis omitting Flaherty et al from the NMA.

A7. In section 4.10.17 of the CS a justification is given for the use of the fixed effect NMA model. Please can you provide results of the model using random-effects, for comparison.

A8. In section 4.10.17 of the CS it is stated that the Bucher method was used to assess consistency between direct and indirect evidence. Please provide summary estimates for the direct and indirect evidence for inspection of consistency (e.g. the 1/AFT with 95% CrI for both PFS and OS). Please give this for fixed and random effects models.

A9. What was the rationale for only including studies of patients who are treatment naive when presenting with metastatic disease in the NMA? (As stated in CS, Table 19).

A10. In section 4.14 of the CS, it is stated that there are no additional ongoing studies (page 96). Were searches for ongoing studies conducted? If so please provide details of the search sources and dates.

A11. Please report the sources used for hand searching in the literature search for the NMA (CS, Figure 35).

A12. Appendix 7 of the CS only provides Hazard Ratio (HR) and AFT values for OS, please could you provide equivalent values for PFS.

Section B: Clarification on cost-effectiveness data

B1. Please clarify how the health state costs for PFS and Progressed Disease (PD) of £378/month were derived.

B2. **Priority question:** Please provide more details of the EQ-5D utility values in the co-BRIM trial. Please provide the number of observations and mean utility scores at each time point, including baseline, for the patients for both arms, and for each category (PFS cobimetinib + vemurafenib; PFS vemurafenib; PD cobimetinib + vemurafenib; PD vemurafenib).

B3. The mean time on treatment reported in Table 40 of the CS (9.9 months) for vemurafenib differs from the value used in the economic model (11.3 months). Please clarify which is the correct value.

B4. Please provide details of the patient characteristics of those in the SEER (Surveillance, Epidemiology, and End Results) database referred to in CS page 108.

B5. Please provide details on how the cure rate on page 109 of the CS has been calculated?

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B6. Please provide AIC / BIC values for the parametric curves for time on treatment, CS page 126.

Section C: Textual clarifications and additional points

C1. Please clarify what the '†' symbols mean in Figure 11, adjacent to the BRIM-3, COMBI-d and BREAK-3 trials.

Single technology appraisal

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

Response to clarification questions

Dear Joanna,

Please find below responses to the clarification questions received from the Evidence Review Group, Southampton Health Technology Assessments Centre, for the above appraisal.

Our responses include academic in confidence information as highlighted below. We therefore also include a redacted version of these responses and the confidential information checklist.

As highlighted within our company submission (CS) on page 42 table 8; various data-cut analyses were conducted during the coBRIM study, for efficacy and safety endpoints. As per our pre-submission correspondence, along with page 85 of the CS, an additional safety analysis of the study was anticipated to be available within Q1 of 2016. These data were not available for our submission on 5th Feb 2016, but have subsequently become available. A summary of the status of the data cuts, related publications, CSR versions and inclusion of the data cuts within our submission and economic model is presented in Table 1 below.

Table 1 Summary of coBRIM data analyses

Conducted and planned analyses	Data cutoff dates	Publications	CSR	Included in CS and economic model
Primary Endpoint (PFS)				
Primary analysis of PFS	9th May 2014	Larkin et al NEJM 2014, SmPC	November 2014 (Research Report 1060643)	CS
Updated analysis of PFS	16th January 2015	Larkin et al ASCO 2015, SmPC	February 2016 (Research Report 1067294)	CS and economic model
Secondary endpoints (OS)				
1st interim analysis of OS	9th May 2014	Larkin et al NEJM 2014, SmPC	November 2014 (Research Report 1060643)	CS
2nd interim analysis of OS	16th January 2015	Larkin et al ASCO 2015, SmPC		CS
Final analysis of OS	28th August 2015	Atkinson et al SMR 2015	February 2016 (Research Report 1067294)	CS and economic model
Safety analyses				
Primary analysis	9th May 2014	Larkin et al NEJM 2014	November 2014 (Research Report 1060643)	CS
Updated analysis	19th September 2014	Dreno et al SMR 2014		CS and economic model*

Final analysis	30th September 2015		February 2016 (Research Report 1067294)	Not included

* Incidence of adverse events incorporated into economic model taken from updated analysis conducted September 2014 and published at SMR congress, Dreno 2014. CS discussion on safety data includes both primary analysis and updated analysis

The November 2014 CSR (Research Report 1060643) was provided at submission on 5th February 2016. With the subsequent availability of the most recent CSR (February 2016, Research Report 1067294), we now also now provide this file.

As the final OS data were available at the time of our CS, the only data points which are not based on the latest available evidence at this point in time (i.e. from the final CSR) are the safety data. Review of the grade ≥3 adverse events shows little difference in the incidence between the November 2014 CSR and the final CSR (Table 2 and Table 3 below). Taking into account this information, and the minimal impact AE costs contribute to the overall ICER, the economic model and CS have not been updated with the latest safety data.

Table 2 Grade ≥3 adverse events occurring in at least 2% of patients in either arm (primary analysis, data cut May 2014) (page 115 of CSR 1060643)

	Vemurafenib + Placebo (N=239)	Vemurafenib + Cobimetinib (N=254)	All Patients (N=493)
MedDRA Preferred Term for Grade 3 events			
GAMMA-GLUTAMYLTRANSFERASE INCREASED	25 (10.5%)	30 (11.8%)	55 (11.2%)
ALANINE AMINOTRANSFERASE INCREASED	15 (6.3%)	29 (11.4%)*	44 (8.9%)
SQUAMOUS CELL CARCINOMA OF SKIN	27 (11.3%)*	6 (2.4%)	33 (6.7%)
RASH MACULO-PAPULAR	13 (5.4%)	16 (6.3%)	29 (5.9%)
RASH	12 (5.0%)	15 (5.9%)	27 (5.5%)
ASPARTATE AMINOTRANSFERASE INCREASED	5 (2.1%)	21 (8.3%)*	26 (5.3%)
BLOOD CREATINE PHOSPHOKINASE INCREASED	0	26 (10.2%)*	26 (5.3%)
KERATOACANTHOMA	18 (7.5%)*	2 (0.8%)	20 (4.1%)
ARTHRALGIA	12 (5.0%)*	6 (2.4%)	18 (3.7%)
FATIGUE	8 (3.3%)	10 (3.9%)	18 (3.7%)
DIARRHEA	0	16 (6.3%)*	16 (3.2%)
HYPERTENSION	6 (2.5%)	10 (3.9%)	16 (3.2%)
BASAL CELL CARCINOMA	5 (2.1%)	10 (3.9%)	15 (3.0%)
BLOOD ALKALINE PHOSPHATASE INCREASED	4 (1.7%)	11 (4.3%)*	15 (3.0%)
DERMATITIS ACNEIFORM	4 (1.7%)	6 (2.4%)	10 (2.0%)
PAIN IN EXTREMITY	6 (2.5%)	3 (1.2%)	9 (1.8%)
HYPONATREMIA	1 (0.4%)	6 (2.4%)*	7 (1.4%)
MYALGIA	6 (2.5%)*	1 (0.4%)	7 (1.4%)
PHOTOSENSITIVITY REACTION	0	6 (2.4%)*	6 (1.2%)
RETINAL DETACHMENT	0	6 (2.4%)*	6 (1.2%)
HYPERKERATOSIS	5 (2.1%)*	0	5 (1.0%)

*Asterisks indicate the population in which the Grade ≥ 3 AE occurred at a higher incidence (>2% difference in incidence between arms).

Table 3 Grade ≥3 adverse events occurring in at least 2% of patients in either arm (final analysis, data cut August 2015) (page 70 of CSR 1067294)

MedDRA Preferred Term	Vemurafenib + Placebo (N=246)	Vemurafenib + Cobimetinib (N=247)	All Patients (N=493)
Total number of patients with at least one adverse event	151 (61.4%)	186 (75.3%)	337 (68.4%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	25 (10.2%)	36 (14.6%)a	61 (12.4%)
ALANINE AMINOTRANSFERASE INCREASED	15 (6.1%)	28 (11.3%)a	43 (8.7%)
SQUAMOUS CELL CARCINOMA OF SKIN	31 (12.6%)a	9 (3.6%)	40 (8.1%)
BLOOD CREATINE PHOSPHOKINASE INCREASED	1 (0.4%)	30 (12.1%)a	31 (6.3%)
RASH MACULO-PAPULAR	13 (5.3%)	18 (7.3%)a	31 (6.3%)
ASPARTATE AMINOTRANSFERASE INCREASED	5 (2.0%)	22 (8.9%)a	27 (5.5%)
RASH	14 (5.7%)	13 (5.3%)	27 (5.5%)
KERATOACANTHOMA	21 (8.5%)a	3 (1.2%)	24 (4.9%)
HYPERTENSION	7 (2.8%)	15 (6.1%)a	22 (4.5%)
BASAL CELL CARCINOMA	6 (2.4%)	14 (5.7%)a	20 (4.1%)
ARTHRALGIA	12 (4.9%)a	6 (2.4%)	18 (3.7%)
DIARRHOEA	2 (0.8%)	16 (6.5%)a	18 (3.7%)
FATIGUE	7 (2.8%)	11 (4.5%)	18 (3.7%)
BLOOD ALKALINE PHOSPHATASE INCREASED	4 (1.6%)	12 (4.9%)a	16 (3.2%)
ANAEMIA	7 (2.8%)	4 (1.6%)	11 (2.2%)
LIPASE INCREASED	2 (0.8%)	8 (3.2%)a	10 (2.0%)
DERMATITIS ACNEIFORM	3 (1.2%)	6 (2.4%)	9 (1.8%)
PAIN IN EXTREMITY	6 (2.4%)	3 (1.2%)	9 (1.8%)
ASTHENIA	3 (1.2%)	5 (2.0%)	8 (1.6%)
EJECTION FRACTION DECREASED	3 (1.2%)	5 (2.0%)	8 (1.6%)
HYPOKALAEMIA	4 (1.6%)	4 (1.6%)	8 (1.6%)
HYPONATRAEMIA	1 (0.4%)	7 (2.8%)a	8 (1.6%)
PHOTOSENSITIVITY REACTION	0	8 (3.2%)a	8 (1.6%)
HYPERKERATOSIS	6 (2.4%)a	1 (0.4%)	7 (1.4%)
MYALGIA	6 (2.4%)a	1 (0.4%)	7 (1.4%)

[a] Indicates the patients in which the Grade ≥ 3 AE occurred at a higher incidence (≥ 2% difference between arms).

A1. Please provide a breakdown of reasons for patients' withdrawal for both treatment arms, as well as the reason for the physician's decision to withdraw patients in the vemurafenib + cobimetinib treatment arm of the coBRIM trial (Table 13, page 59).

Information on the reason for patient withdrawal, or physician decision to withdraw patients were not collected during the coBRIM study (Larkin et al. 2014). Table 13, page 59 in the CS refers to withdrawal by subjects at any point post study randomisation, including after the patient may have stopped study treatment.

Reasons for patient discontinuation from study treatment, at the clinical cut off for primary efficacy analysis (9th May 2014) are provided in Table 4 below.

Table 4 Primary reason for patients discontinued from study treatment

Status	Vemurafenib + Placebo (N=239)	Vemurafenib + Cobimetinib (N=254)	ALL Patients (N=493)
Patients Discontinued from Cobimetinib or Placebo			
Treated	239 (100.0%)	254 (100.0%)	493 (100.0%)
Patients still on treatment	99 (41.4%)	147 (57.9%)	246 (49.9%)
Patients discontinued treatment	140 (58.6%)	107 (42.1%)	247 (50.1%)
Adverse Event	19 (7.9%)	35 (13.8%)	54 (11.0%)
Pregnancy	1 (0.4%)	0	1 (0.2%)
Death	0	2 (0.8%)	2 (0.4%)
Lost To Follow-Up	1 (0.4%)	0	1 (0.2%)
Protocol Violation	0	0	0
Non-Compliance With Study Drug	1 (0.4%)	1 (0.4%)	2 (0.4%)
Non-Compliance	0	2 (0.8%)	2 (0.4%)
Withdrawal By Subject	2 (0.8%)	2 (0.8%)	4 (0.8%)
Study Terminated By Sponsor	0	0	0
Physician Decision	1 (0.4%)	3 (1.2%)	4 (0.8%)
Progression Of Disease	113 (47.3%)	62 (24.4%)	175 (35.5%)
Other	2 (0.8%)	0	2 (0.4%)
Patients Discontinued from Vemurafenib			
Treated	239 (100.0%)	254 (100.0%)	493 (100.0%)
Patients still on treatment	100 (41.8%)	150 (59.1%)	250 (50.7%)
Patients discontinued treatment	139 (58.2%)	104 (40.9%)	243 (49.3%)
Adverse Event	21 (8.8%)	30 (11.8%)	51 (10.3%)
Pregnancy	1 (0.4%)	0	1 (0.2%)
Death	1 (0.4%)	3 (1.2%)	4 (0.8%)
Lost To Follow-Up	1 (0.4%)	0	1 (0.2%)
Protocol Violation	0	0	0
Non-Compliance With Study Drug	1 (0.4%)	1 (0.4%)	2 (0.4%)
Non-Compliance	0	2 (0.8%)	2 (0.4%)
Withdrawal By Subject	2 (0.8%)	2 (0.8%)	4 (0.8%)
Study Terminated By Sponsor	0	0	0
Physician Decision	0	2 (0.8%)	2 (0.4%)
Progression Of Disease	112 (46.9%)	64 (25.2%)	176 (35.7%)
Patients Discontinued from Vemurafenib and Cobimetininb/Placebo			
Treated	239 (100.0%)	254 (100.0%)	493 (100.0%)
Discontinued both treatments	138 (57.7%)	102 (40.2%)	240 (48.7%)
Adverse Event	17 (7.1%)	27 (10.6%)	44 (8.9%)
Progression Of Disease	112 (46.9%)	62 (24.4%)	174 (35.3%)
Death	0	2 (0.8%)	2 (0.4%)
Other	9 (3.8%)	11 (4.3%)	20 (4.1%)

A2. The clinical study report (CSR) (section 3.10.8) states that sensitivity analyses were conducted for progression free survival (PFS) (3 analyses) and overall survival (OS) (2 analyses) but in the company submission (CS) (page 54) only the PFS sensitivity analyses are mentioned, not the OS ones. The CS states that the sensitivity analyses had no impact on results for PFS, but since the OS sensitivity analyses are not mentioned it's not clear whether these affected results or not. Please could you provide the results of these analyses, or provide a statement regarding the results of the OS sensitivity analyses.

Planned sensitivity analyses:
Sensitivity analyses for PFS and OS were planned as detailed below. Not all planned sensitivity analyses were conducted. Where this is the case, explanation for non-completion of the analyses is included.

Progression-Free Survival – Planned analyses

The following sensitivity analyses of PFS were planned:

1. **PFS non-stratified analysis**: Non-stratified analyses of treatment effect (log-rank test and HR with use of a Cox proportional hazards model).

   As compared to the base-case primary efficacy analysis: two-sided stratified log-rank test at an overall 0.05 significance level (HR estimated using a stratified Cox model).

2. **PFS censored for non-protocol anti-cancer therapy:** Patients who died or progressed after having received non-protocol anti-cancer therapy were to be censored at the date of the last evaluable tumour assessment prior to start of non-protocol anti-cancer therapy. Unstratified and stratified analyses of PFS were planned.

   Base-case, primary efficacy analysis incorporated 2 stratification factors: geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; M1c).
   In the base-case analysis, two instances of censoring were planned: patients who have not experienced disease progression or death were censored at the last tumor assessment date, or patients with no post-baseline tumor assessment were censored at the randomization date.

3. **PFS censoring accounting for missed visits:** Patients who died or progressed after two or more consecutive missed visits were to be censored at the date of the last evaluable tumour assessment. Unstratified and stratified analyses of PFS were planned.

   Base-case, primary efficacy analysis incorporated 2 stratification factors: geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; M1c).
   In the base-case analysis, two instances of censoring were planned: patients who have not experienced disease progression or death were censored at the last tumor assessment date, or patients with no post-baseline tumor assessment were censored at the randomization date.

Results of the PFS sensitivity analyses:

Primary efficacy analysis (from May 2014 data cut) are presented in Table 5 below to allow comparison with the sensitivity analyses. In the submission base-case scenario, PFS results are taken from the updated efficacy analysis using the data cut off 16th January 2015. However sensitivity analyses were conducted at the primary efficacy analysis only. For clarity of comparison, updated results from Jan 2014 are not included in Table 5.

Table 5 Primary analyses of PFS by investigator assessment

End point	Vemurafenib and placebo (n=248)	Cobimetinib and vemurafenib (n=247)
Primary Outcome		
Data cutoff: 9 May 2014 PFS according to investigator assessment * Median follow-up, months Median duration, months (95% CI) Hazard ratio for death or disease progression (95% CI) P value	 7.3 6.2 (5.6–7.4) Reference Reference	 7.3 9.9 (9.0–NR) 0.51 (0.39–0.68) <0.001

* Patients were stratified according to geographic region and metastasis classification

1. **PFS non-stratified analysis**:

   A non-stratified analysis of PFS showed results similar to the stratified analysis with HR in favour of the vemurafenib + cobimetinib arm (HR = 0.51; 95% CI: 0.39-0.89; p<0.001) (Table 6).The median PFS was 9.9 months (95% CI: 9.9-upper bound not reached) in the vemurafenib + cobimetinib arm and 6.2 months (95% CI: 5.6-7.4) in the vemurafenib + placebo arm.

Table 6 - Sensitivity analysis of PFS without stratification (ITT population) (Primary CSR p603)

End point	Vemurafenib + placebo (n=248)	Vemurafenib + cobimetinib (n=247)
Data cutoff: 9 May 2014 PFS according to investigator assessment Median duration, months (95% CI) Hazard ratio for death or disease progression (95% CI) P value	 6.2 (5.6–7.4) Reference Reference	 9.9 (9.0–NE) 0.51 (0.39–0.68) <0.001

NE=not evaluable

2. **PFS censored for non-protocol anti-cancer therapy:**

   Unstratified and stratified analyses of PFS for non-protocol anti-cancer therapy are shown in Table 7 and Table 8 below.

Table 7 - Sensitivity analysis of PFS censored at the time of using non-protocol anti-cancer therapy with stratifications (ITT population) (Primary CSR p605)

End point	Vemurafenib + placebo (n=248)	Vemurafenib + cobimetinib (n=247)
PFS censored by anti-cancer therapy		
Data cutoff: 9 May 2014 PFS Median duration, months (95% CI)	 6.2 (5.6–7.5)	 11.14 (9.0–NE)
Stratified analysis by geographic region and metastasis classification		
Hazard ratio for death or disease progression (95% CI) P value	Reference Reference	0.51 (0.38–0.67) p<0.0001

NE=not evaluable

Table 8 - Sensitivity analysis of PFS censored at time of using non-protocol anti-cancer therapy without stratifications (ITT population) (Primary CSR p606)

End point	Vemurafenib + placebo (n=248)	Vemurafenib + cobimetinib (n=247)
PFS censored by anti-cancer therapy		
Data cutoff: 9 May 2014 PFS Median duration, months (95% CI)	 6.2 (5.6–7.5)	 11.1 (9.0–NE)
Unstratified analysis		
Hazard ratio for death or disease progression (95% CI) P value	Reference Reference	0.51 (0.38–0.68) p<0.0001

NE=not evaluable

3. **PFS censoring accounting for missed visits:**

   The sensitivity analysis of PFS censored for missing visits was not performed as the number of patients with missing visits was very low (p69 primary CSR)

Overall Survival – Planned analyses

The following sensitivity analyses of OS were planned:

1. **Non-stratified OS analysis**: Non-stratified analyses of treatment effect (log-rank test and HR with use of a Cox proportional hazards model) for the ITT population.

   As compared to the base-case OS analysis: two-sided stratified log-rank test at an overall two-sided 0.05 significance level (HR for death estimated using a stratified Cox model)

2. **OS censored for subsequent anti-cancer therapy**: Unstratified and stratified analyses of OS censored for use of subsequent anti-cancer therapy for the ITT population. For this analysis, OS times for patients in either treatment arm who received any anti-cancer therapy subsequent to the treatment assigned by randomisation were to be imputed from the date of start of the subsequent anticancer therapy (including cobimetinib for patients in the vemurafenib treatment arm) according to a range assumed effect.

   This analysis was planned, whilst recognising cross-over to cobimetinib for patients randomised to vemurafenib + placebo would have constituted a protocol violation.

Results of the OS sensitivity analyses:

In the submission base-case scenario, OS results are from the final OS data cutoff – 28th August 2015. OS analysis from the final OS data cut is presented in Table 9 to allow comparison with the sensitivity analyses, which were also conducted at this data cut off.

Table 9 Updated analyses of OS by investigator assessment

End Point	Vemurafenib + placebo n = 247	Vemurafenib + cobimetinib n = 247
Data cutoff: 28 August 2015 (**used as submission base case**)		

Overall survival * Median duration, months (95% CI)	17.4 (15.0-19.8)	22.3 (20.3-NE)
Hazard ratio for death (95% CI)	Reference	0.70 (0.55-0.90)
p value	Reference	p=0.005

1. Non-stratified OS analysis:

   A non-stratified analysis of final OS showed results similar to the stratified analysis with HR in favour of the vemurafenib + cobimetinib arm (HR = 0.70; 95% CI: 0.54-0.89; p=0.0037) (Table 10).The median OS was 22.3 months (95% CI: 20.3-upper bound not reached) in the vemurafenib + cobimetinib arm and 17.4 months (95% CI: 15.0-19.8) in the vemurafenib + placebo arm. (p50 and 1253 final CSR)

Table 10 - Analysis of Overall Survival without Stratifications (ITT population)

End point	**Vemurafenib + placebo (n=248)**	**Vemurafenib + cobimetinib (n=247)**
OS		
Data cutoff: 28 August 2015 OS Median duration, months (95% CI)	17.4 (15.0-19.8)	22.3 (20.3-NE)
Unstratified analysis		
Hazard ratio for death or disease progression (95% CI) P value	Reference Reference	0.70 (0.54-0.89) p=0.0037

NE=not evaluable

2. **OS censored for subsequent anti-cancer therapy**:

   Sensitivity analysis for OS accounting for subsequent anti-cancer therapy was not conducted because there were no patients in the vemurafenib + placebo arm who had crossed over to cobimetinib at the time of the final OS analysis.

A3. The CSR (section 3.10.16.2) states that a sensitivity analysis of PFS censored for missing visits was not performed as the number of patients with missing visits was very low. However, the CS (page 54) implies this sensitivity analysis was performed and showed no impact on the results from the primary analysis. Please explain this discrepancy.

As outlined in A2, a sensitivity analysis of PFS censored for missing visits was planned. It was not however conducted as the number of patients with missing visits was very low. Section 4.4 of the CS should have read:

PFS censoring accounting for missed visits: Patients who died or progressed after two or more consecutive missed visits were censored at the date of the last evaluable tumour assessment. Unstratified and stratified analyses of PFS were ***planned***.

A4. In section 4.10.4 of the CS (Indirect and mixed treatment comparisons), it is stated that 29 unique trials were identified from 35 publications. The PRISMA flowchart in Appendix 4 (Figure 35) shows that there were 33 publications of 25 unique RCTs. Please clarify this discrepancy in figures for publications and trials. Please supply a list of references for all of the publications included in the NMA, highlighting those references that were included in the 'restricted network' of BRAF mutation positive studies.

The final systematic review identified a total of 35 publications covering 27 unique RCTs, with 2 additional publications identified during hand searching. Therefore the final, complete systematic literature review identified 37 publications of 29 unique trials. Three publications were excluded as they did not report outcomes of interest.

The discrepancies in the body text and PRISMA flowchart are due to typographical errors when transcribing from draft versions of the systematic review report. This error does not have any effect on the resulting network meta-analysis, as all included studies are accounted for.

The full list of identified publications is presented in Table 11. Those studies included in the network meta-analysis (NMA) are highlighted in bold.

Table 11 List of publications identified in the clinical systematic literature review

No.	Study ID	Comments
1	Avril MF, Aamdal S, Grob JJ et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: A phase III study. Journal of Clinical Oncology. 2004;22(6):1118-25	
2	Bafaloukos D, Tsoutsos D, Kalofonos H,et al. Temozolomide and cisplatin versus temozolomide in patients with advanced melanoma: a randomized phase II study of the Hellenic Cooperative Oncology Group. Annals of oncology. 2005 Jun;16(6):950-7.	
3	Bajetta E, Di Leo A, Zampino MG, Sertoli MR, Comella G, Barduagni M, Giannotti B, Queirolo P, Tribbia G, Bernengo MG, et al. Multicenter randomized trial of dacarbazine alone or in combination with two different doses and schedules of interferon alfa-2a in the treatment of advanced melanoma. J Clin Oncol. 1994 Apr; 12(4):806-11.	
4	**Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. The New England journal of medicine. 2011 Jun 30; 364(26):2507-16.**	**Linked to McArthur 2014 and Chapman 2012** **(BRIM 3 study)**
5	**Chapman PB. Et al. Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAFV600E-mutated melanoma. J Clin Oncol 30, 2012 (suppl;abstr 8502).**	**Linked to McArthur 2014 and Chapman 2011** **(BRIM 3 study)**
6	Cocconi G, Bella M, Calabresi F, Tonato M, Canaletti R, Boni C, et al. Treatment of metastatic malignant melanoma with dacarbazine plus tamoxifen. New England journal of medicine. 1992 Aug; 327(8):516-23.	
7	Danson, S., et al. (2003). "Randomized phase II study of temozolomide given every 8 hours or daily with either interferon alfa-2b or thalidomide in metastatic malignant melanoma." Journal of clinical oncology 21(13): 2551-2557.	
8	Daponte, A. Phase III randomized study of fotemustine and dacarbazine versus dacarbazine with or without interferon-a in advanced malignant melanoma. Journal of Translational Medicine 2013; 11:38.	

No.	Study ID	Comments
9	Falkson CI, Ibrahim J, Kirkwood JM, Coates AS, Atkins MB, Blum RH. Phase III trial of dacarbazine versus dacarbazine with interferon alpha-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon alpha-2b and tamoxifen in patients with metastatic malignant melanoma: an Eastern Cooperative Oncology Group study. Journal of clinical oncology. 1998 May; 16(5):1743-51.	
10	Falkson CI, Falkson G, Falkson HC. Improved results with the addition of interferon alfa-2b to dacarbazine in the treatment of patients with metastatic malignant melanoma. Journal of clinical oncology. 1991 Aug; 9(8):1403-8.	
11	**Flaherty, K. T., et al. (2012). "Improved survival with MEK inhibition in BRAF-mutated melanoma." New England journal of medicine 367(2): 107-114.**	
12	**Flaherty, K. T., et al. (2012). "Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations." The New England journal of medicine 367(18): 1694-1703.**	
13	**Hauschild, A, Grob, JJ, Demidov, LV, Jouary, T. Gutzmer, R. Millward, M. et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012 Jul; 380(9839):358-65.**	**Linked to Hauschild, 2013** **(BREAK 3 study)**
14	**Hauschild, A., et al. An update on BREAK-3, a Phase III, randomized trial: dabrafenib vs dacarbazine (DTIC) in patients with BRAF V600E positive mutation metastatic melanoma (MM). ASCO 2013; Abstract no. 9013.**	**Linked to Hauschild 2012** **(BREAK 3 study)**
15	Hersh EM, O'Day SJ, Powderly J, Khan KD, Pavlick AC, Cranmer LD, Samlowski WE, Nichol GM, Yellin MJ, Weber JS. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naïve patients with advanced melanoma. Invest New Drugs. 2011 Jun; 29(3):489-98.	
16	Hodi, S. Postow, M. A. Chesney, J. A. Pavlick, A. C. Robert, C. Grossmann, K. F. et al. Clinical response, progression-free survival (PFS), ad safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 069 study. J Clin Oncol 33, 2015; (suppl; abstr 9004).	Linked to Postow 2015
17	Kaufmann R, Spieth K, Leiter U, Mauch C, von den Driesch P, Vogt T, et al. Temozolomide in combination with interferon-alfa versus temozolomide alone in patients with advanced metastatic melanoma: a randomized, phase III, multicenter study from the Dermatologic Cooperative Oncology Group. Journal of clinical oncology. 2005 Dec; 23(35):9001-7.	
18	**Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. The New England journal of medicine. 2014 Nov 13; 371(20):1867-76.**	**(coBRIM study)**
19	Larkin, J. Chiarion-Sileni, V. Gonzalez, R. Grob, J. J. Cowey, C. L. Lao, C. D. Schadendorf, D. Dummer, R. Smylie, M. et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. The New England Journal of Medicine, May 31, 2015.	
20	**Long G.V. Stroyakovskiy, D. Gogas, H. Levchenko, E. et al. Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma. New England Journal of Medicine 2014; 371:1877-88.**	**Linked to Long 2015** **(COMBI-d study)**
21	**Long, G. V. Stroyakovskiy, D. Gogas, H. Levchenko, E. et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. The Lancet, May 31, 2015.**	**Linked to Long 2014** **(COMBI-d study)**
22	Maio, M. Five year survival rates for treatment-naïve patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol 2015 Apr 1; 33(10):1191-6.	Linked to Robert 2011 and Thomas 2012

No.	Study ID	Comments
23	**McArthur, G. A. et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. The Lancet 2014; 3:323-32.**	**Linked to Chapman 2011 and Chapman 2012** **(BRIM 3 study)**
24	Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. Journal of clinical oncology. 2000 Jan; 18(1):158-66.	
25	Patel PM, Suciu S, Mortier L, Kruit WH, Robert C, Schadendorf D, Trefzer U, Punt CJ, Dummer R, Davidson N, Becker J, Conry R, Thompson JA, Hwu WJ, Engelen K, Agarwala SS, Keilholz U, Eggermont AM, Spatz A; EORTC Melanoma Group. Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV melanoma: final results of a randomized phase III study (EORTC 18032). Eur J Cancer. 2011 Jul;47(10):1476-83.	
26	Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, Linette GP, Meyer N, et al. Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. DOI: 10.1056/NEJMoa1414428. April 20, 2015, at NEJM.org.	Linked to Hodi 2015
27	Richtig, E., et al. (2004). "Temozolomide and interferon alpha 2b in metastatic melanoma stage IV." British journal of dermatology 151(1): 91-98.	
28	**Robert, C., Karaszewska, B., Schachter, J., Rutkowski, P., Mackiewicz, A., Stroiakovski, D., Lichinitser, M., Dummer, R., Grange, F., Mortier, L., Chiarion-Sileni, V et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. N Engl J Med 2015; 372:30-9.**	
29	Robert, C., Thomas, L., Bondarenko, I., O'Day, S., Weber, J., Garbe, C., Lebbe, C., Baurain, J. F., Testori, A., Grob, J. J., Davidson, N., Richards, J., Maio, M et al. Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. N Engl J Med 2011; 364:2517-26.	Linked to Maio 2013 and Thomas 2012
30	Robert, C. et al. Nivolumab in previously untreated melanoma without BRAF mutation. The New England Journal of Medicine 2015; 372:4:320-330.	
31	Robert, C. Schachter, J. Long, G. Arance, A. Pembrolizumab versus ipilimumab in advanced melanoma. The New England Journal of Medicine April 19, 2015.	
32	Schadendorf D, Amonkar MM, Stroyakovskiy D, Levchenko E, Gogas H, de Braud F, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. Eur J Cancer. 2015 May;51(7):833-40. PubMed PMID: 25794603.	Publication excluded as outcomes not of interest Linked to Long 2014 and Long 2015 (COMBI-d study)
33	Schiller JH, Pugh M, Kirkwood JM, Karp D, Larson M, Borden E. Eastern cooperative group trial of interferon gamma in metastatic melanoma: an innovative study design. Clin Cancer Res. 1996 Jan;2(1):29-36	Publication excluded as outcomes not of interest
34	Thomas, L. et al. Safety of ipilimumab in patients (pts) with untreated, advanced melanoma alive beyond 2 years: Results from a phase III study. J Clin Oncol 30, 2012 (suppl; abstr 8512).	Publication excluded as outcomes not of interest Linked to Robert 2011 and Maio 2013
35	Thomson DB, Adena M, McLeod GRC, Hersey P, Gill PG, Coates AS, et al. Interferon-alpha2a does not improve response or survival when combined with dacarbazine in metastatic malignant melanoma: Results of a multi-institutional Australian randomized trial. Melanoma research. 1993;3(2):133-8.	
36	Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010 Feb;11(2):155-64	

No.	Study ID	Comments
37	Young AM, Marsden J, Goodman A, Burton A, Dunn JA. Prospective randomized comparison of dacarbazine (DTIC) versus DTIC plus interferon-alpha (IFN-alpha) in metastatic melanoma. Clinical oncology (Royal College of Radiologists (Great Britain)). 2001; 13(6):458-65.	

A5. Priority question. In section 4.10.12 of the CS it is stated that "Evidence from a previously conducted NMA (Bexelius 2014) found the accelerated failure time (AFT) survival model was a better fit compared with the proportional hazards (PH) model, for trials in metastatic melanoma" There is no entry in the reference list for Bexelius 2014 and no full publication has been provided. Please can you supply the citation and the full text.

Citation: *Bexelius C, Quigley J, Thuresson P-O, Hawkins N. The Comparative Efficacy of First-Line Treatments for Stage IIIC and Stage IV Melanoma: Results of a Systematic Review and Network Meta-Analysis. European Society for Medical Oncology (ESMO) congress 2014 - Poster presentation 1095P*. The reference file has been submitted to NICE Docs as part of this response.

A6. Priority question. In section 4.10.12 of the CS the main assumption for the NMA is stated to be that the treatment node of dacarbazine or paclitaxel in the Flaherty trial is considered to interact in the same way as dacarbazine in other trials. Please state the justification for this assumption, and provide a sensitivity analysis omitting Flaherty et al from the NMA.

The NMA was conducted to support pricing and reimbursement submissions across all markets, and so included comparators not listed in the final NICE scope. The NMA included a scenario which restricted the evidence base to only include those studies reporting on patients who were BRAF mutation positive (i.e. no inclusion of patients with wild-type status). This scenario was considered most appropriate for the appraisal scope. This scenario produced a small but connected network, which allowed comparison between cobimetinib + vemurafenib and dabrafenib.

In order to build a connected network of evidence restricted to BRAF mutation positive patients, the treatment node of dacarbazine or paclitaxel in the Flaherty trial was considered to interact in the same way as dacarbazine in other melanoma trials. This allowed connection of the Flaherty trial, which assessed the efficacy of trametinib 2mg compared to dacarbazine or paclitaxel.

The assumption that dacarbazine and paclitaxel interact in the same way is supported by reviews of phase II study results, which show comparable efficacy of paclitaxel to dacarbazine in the treatment of melanoma (Kaufmann H, 2016). Additionally, this assumption is made within the Flaherty study as study results are not stratified for chemotherapy treatment choice (dacarbazine or paclitaxel), thus assuming an equivalent activity in melanoma.

It is acknowledged that this indirect comparison, of trametinib with cobimetinib + vemurafenib, was not required in order to meet the appraisal scope (for which the comparators were vemurafenib or dabrafenib monotherapy). Sensitivity analyses were

performed removing the Flaherty 2012b study from the network, as presented in Figure 1 and Figure 2. The removed study contributed an additional node to the network: trametinib 2mg was not directly connected to any other treatment in the network, meaning the Flaherty 2012b study provides direct evidence on the dacarbazine - trametinib 2mg comparison, but does not provide indirect evidence on any of the remaining comparisons. Therefore, removal of the Flaherty 2012b study from the network does not alter the effect estimates of the comparisons not involving trametinib 2mg.

The results of this newly-performed sensitivity analysis are as anticipated, with these being almost identical to the base case NMA; the results only showing changes in the second decimal due to the Monte Carlo error. Results are displayed for OS in Table 12 and Figure 3, and for PFS in Table 13 and Figure 4 below

Figure 1 Network of evidence for OS and PFS in studies reporting the BRAF mutation status of patients, including Flaherty 2012b study (blue box represents treatment of interest)

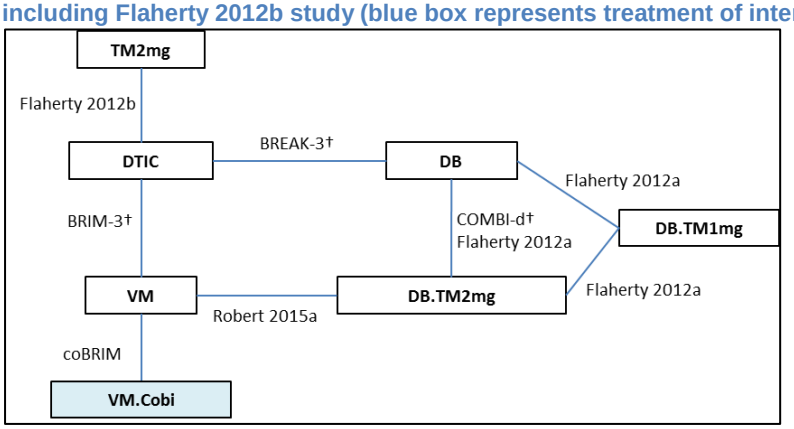
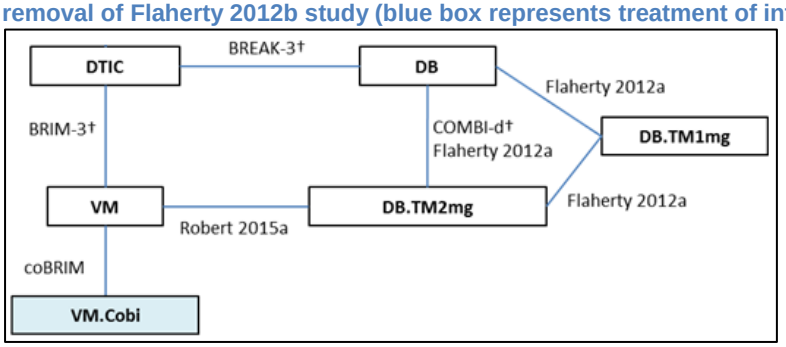


Figure 2 Network of evidence for OS and PFS in studies reporting the BRAF mutation status of patients, removal of Flaherty 2012b study (blue box represents treatment of interest)



Abbreviations: BD, twice daily; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg DTIC, dacarbazine; OS, overall survival VM, vemurafenib, VM.Cobi, vemurafenib plus cobimetinib † Trial names with more than one publication contributing data for the same trial

Table 12 NMA results reporting 1/AFT (95%CrI) for OS removing Flaherty 2012b study

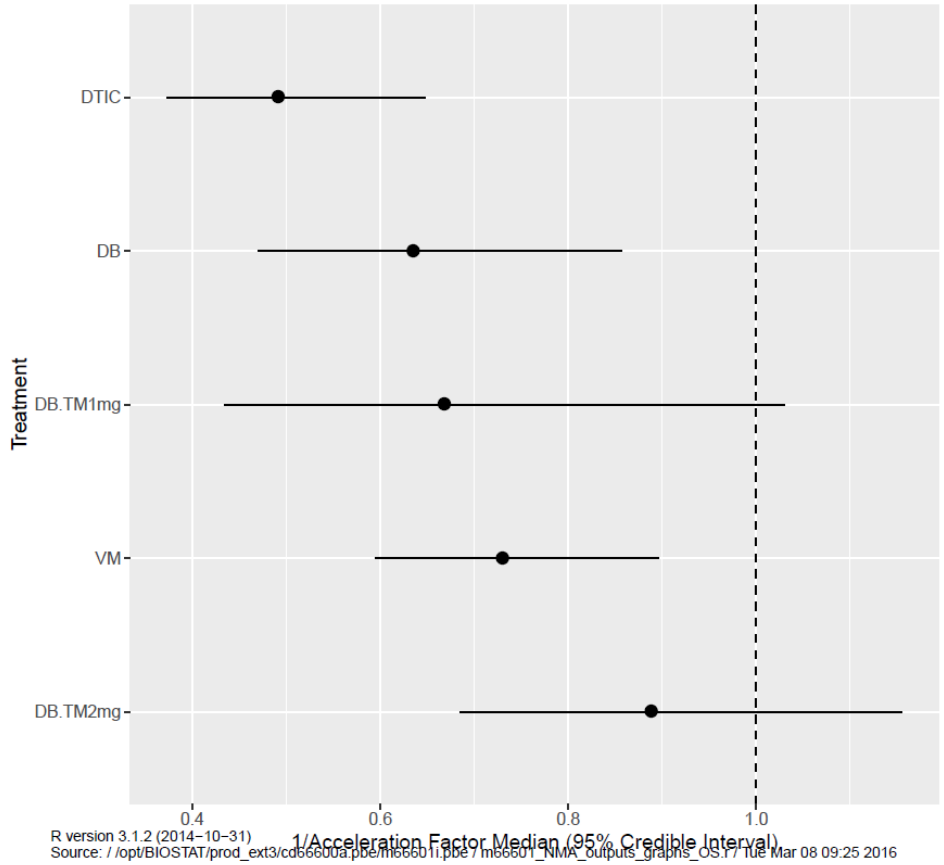
Treatment A	Treatment B					
	DTIC	DB.TM1mg	DB.TM2mg	DB	VM	VM.Cobi
DTIC		1.36 (0.91, 2.03)	**1.81 (1.45, 2.26)**	**1.29 (1.02, 1.64)**	**1.49 (1.24, 1.78)**	**2.03 (1.54, 2.68)**
DB.TM1mg	0.74 (0.49, 1.1)		1.33 (0.93, 1.89)	0.95 (0.67, 1.34)	1.09 (0.75, 1.6)	1.5 (0.97, 2.3)
DB.TM2mg	**0.55 (0.44, 0.69)**	0.75 (0.53, 1.07)		**0.71 (0.6, 0.85)**	**0.82 (0.7, 0.97)**	1.13 (0.87, 1.46)
DB	**0.77 (0.61, 0.98)**	1.05 (0.74, 1.49)	**1.4 (1.17, 1.67)**		1.15 (0.92, 1.43)	**1.57 (1.17, 2.13)**
VM	**0.67 (0.56, 0.81)**	0.92 (0.63, 1.34)	**1.22 (1.03, 1.43)**	0.87 (0.7, 1.08)		**1.37 (1.12, 1.68)**

VM.Cobi	**0.49 (0.37, 0.65)**	0.67 (0.43, 1.03)	0.89 (0.68, 1.16)	**0.64 (0.47, 0.86)**	**0.73 (0.59, 0.9)**	

Results from the NMA are reported in the white cells each as a comparison of Treatment A vs treatment B. Results in bold are considered statistically significant.

Abbreviations: AFT, accelerated time failure; CrI, credible interval; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg; DTIC, dacarbazine; OS, overall survival; VM, vemurafenib; VM.Cobi, vemurafenib plus cobimetinib

Figure 3: Forest plot of the treatment comparison obtained from the NMA for VM.Cobi vs comparators for OS with removal of the Flaherty 2012b study.



Abbreviations: AFT, accelerated time failure; CrI, credible interval; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg; DTIC, dacarbazine; OS, overall survival; VM, vemurafenib; VM.Cobi, vemurafenib plus Cobimetinib

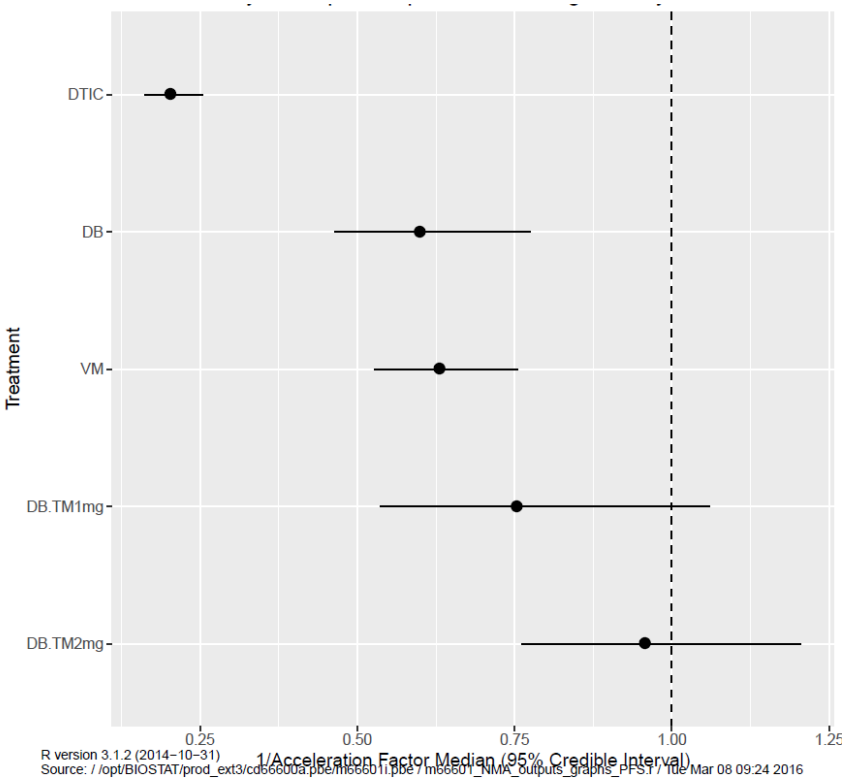
Table 13: NMA results reporting 1/AFT (95%CrI) for PFS removing Flaherty 2012b study

Treatment A	Treatment B					
	DTIC	**DB.TM1mg**	**DB.TM2mg**	**DB**	**VM**	**VM.Cobi**
DTIC		**3.71 (2.76, 5.01)**	**4.72 (3.96, 5.63)**	**2.95 (2.46, 3.56)**	**3.11 (2.72, 3.56)**	**4.93 (3.93, 6.18)**
DB.TM1mg	**0.27 (0.2, 0.36)**		1.27 (0.98, 1.65)	0.8 (0.61, 1.03)	0.84 (0.63, 1.12)	1.33 (0.94, 1.86)
DB.TM2mg	**0.21 (0.18, 0.25)**	0.79 (0.61, 1.02)		**0.63 (0.54, 0.73)**	**0.66 (0.57, 0.76)**	1.04 (0.83, 1.31)
DB	**0.34 (0.28, 0.41)**	1.26 (0.97, 1.63)	**1.6 (1.37, 1.86)**		1.05 (0.88, 1.26)	**1.67 (1.29, 2.15)**
VM	**0.32 (0.28, 0.37)**	1.19 (0.9, 1.59)	**1.52 (1.32, 1.75)**	0.95 (0.79, 1.14)		**1.59 (1.32, 1.9)**
VM.Cobi	**0.2 (0.16, 0.25)**	0.75 (0.54, 1.06)	0.96 (0.76, 1.2)	**0.6 (0.46, 0.77)**	**0.63 (0.53, 0.76)**	

Results from the NMA are reported in the white cells each as a comparison of Treatment A vs treatment B. Results in bold are considered statistically significant.

Abbreviations: AFT, accelerated time failure; CrI, credible interval; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg; DTIC, dacarbazine; OS, overall survival; VM, vemurafenib; VM.Cobi, vemurafenib plus cobimetinib

Figure 4: Forest plot of the treatment comparison obtained from the NMA for VM.Cobi vs comparators for PFS with removal of the Flaherty 2012b study



Abbreviations: AFT, accelerated time failure; CrI, credible interval; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg; DTIC, dacarbazine; OS, overall survival; VM, vemurafenib; VM.Cobi, vemurafenib plus Cobimetinib

A7. In section 4.10.17 of the CS a justification is given for the use of the fixed effect NMA model. Please can you provide results of the model using random-effects, for comparison.

Due to the small network and limited number of studies, a random-effects model will provide a poor estimate of the distribution of intervention effects. The model fit of the fixed- and random-effects models conducted for each outcome was compared using the deviance information criterion (DIC). The DIC values for the base case analyses of PFS and OS indicated that the fixed effects models provided improved model fit compared with the random effect models:

- -20.98 for PFS fixed effect
- -20.43 for PFS random effects

- -15.26 for OS fixed effect
- -14.11 for OS random effects.

As requested the results of the NMA using random-effects are presented for PFS in Table 14 and for OS in Table 15 below. Fixed effect results are included for comparison and results are shown for AFT and HR, against DTIC. As seen in Table 14 and Table 15, the resulting AFT and HR values across the models are broadly consistent.

Table 14 NMA results using fixed effect and random effect models for PFS against DTIC

Analysis	DB	DB.TM1mg	DB.TM2mg	DTIC	TM2mg	VM	VM.Cobi	DTIC
FE_AFT_PFS	0.34 (0.28, 0.41)	0.27 (0.20, 0.36)	0.21 (0.18, 0.25)	1	0.46 (0.36, 0.58)	0.32 (0.28, 0.37)	0.20 (0.16, 0.25)	-20.98
RE_AFT_PFS	0.34 (0.16, 0.77)	0.27 (0.09, 0.85)	0.21 (0.09, 0.51)	1	0.46 (0.18, 1.18)	0.32 (0.15, 0.71)	0.20 (0.06, 0.69)	-20.43
FE_HR_PFS	0.39 (0.31, 0.49)	0.26 (0.17, 0.41)	0.24 (0.20, 0.30)	1	0.42 (0.31, 0.57)	0.44 (0.38, 0.51)	0.26 (0.20, 0.34)	-10.90
RE_HR_PFS	0.39 (0.13, 1.19)	0.26 (0.05, 1.28)	0.22 (0.06, 0.71)	1	0.42 (0.11, 1.57)	0.42 (0.14, 1.22)	0.25 (0.04, 1.32)	-11.72

Abbreviations: AFT, accelerated failure time; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg; DIC, deviance information criterion; DTIC, dacarbazine; FE, fixed effects; HR, hazard ratio; NA, not applicable; NMA, network meta-analysis PFS, progression free survival; RE, random effects; TM2m g, trametinib 2mg; VM, vemurafenib; VM.Cobi, vemurafenib plus cobimetinib

Table 15 NMA results using fixed effect and random effect models for OS against DTIC

Analysis	DB	DB.TM1mg	DB.TM2mg	DTIC	TM2mg	VM	VM.Cobi	DIC
FE_AFT_OS	0.77 (0.61, 0.98)	0.73 (0.49, 1.09)	0.55 (0.44, 0.69)	1	0.64 (0.44, 0.94)	0.67 (0.56, 0.81)	0.49 (0.37, 0.65)	-15.26
RE_AFT_OS	0.79 (0.38, 1.74)	0.75 (0.26, 2.30)	0.57 (0.26, 1.37)	1	0.64 (0.25, 1.62)	0.68 (0.33, 1.46)	0.50 (0.16, 1.62)	-14.11
FE_HR_OS	0.78 (0.58, 1.05)	0.76 (0.40, 1.44)	0.57 (0.44, 0.75)	1	0.56 (0.35, 0.90)	0.79 (0.67, 0.94)	0.55 (0.41, 0.74)	-8.77
RE_HR_OS	0.79 (0.35, 1.79)	0.76 (0.22, 2.54)	0.57 (0.23, 1.38)	1	0.56 (0.21, 1.51)	0.79 (0.36, 1.75)	0.55 (0.16, 1.86)	-7.07

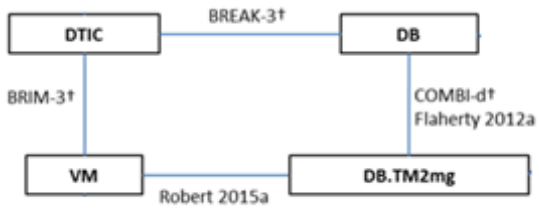
Abbreviations: AFT, accelerated failure time; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg; DIC, deviance information criterion; DTIC, dacarbazine; FE, fixed effects; HR, hazard ratio; NA, not applicable; NMA, network meta-analysis PFS, progression free survival; RE, random effects; TM2m g, trametinib 2mg; VM, vemurafenib; VM.Cobi, vemurafenib plus cobimetinib

A8. In section 4.10.17 of the CS it is stated that the Bucher method was used to assess consistency between direct and indirect evidence. Please provide summary estimates for the direct and indirect evidence for inspection of

consistency (e.g. the 1/AFT with 95% CrI for both PFS and OS). Please give this for fixed and random effects models.

The only closed loop in the network consists of four tratments and five studies, as presented in Figure 5 below. Both a fixed and a random effects model were fit to assess conflict between the indirect and the direct evidence using the Bucher method. Direct estimates from individual trials were used for all comparisons except dabrafenib plus trametinib 2mg (DB.TM2mg) versus dabrafenib (DB), since two trials are available (COMBI-d and Flaherty 2012a). A pair-wise meta-analysis was performed using the Der Simonian-Laird (Der Simonian-Laird, R 1986) estimator for the random effects model.

Figure 5 NMA Closed network



Abbreviations: DB, dabrafenib; DB.TM2mg, dabrafenib plus trametinib 2mg DTIC, dacarbazine; VM, vemurafenib
† Trial names with more than one publication contributing data for the same trial

Table 16 and Table 17 present the results for the direct and indirect evidence to assess consistency for both OS and PFS respectively. NMA results were also included to contextualise the assessment. For OS the estimated variance of the random effects is 0, therefore the random effects estimates is set equal to the fixed effect estimate for the direct evidence in the contrast DB.TM2mg vs DB. Therefore all the effects, fixed and random, coincide.

To test the null hypothesis of no inconsistency the estimated absolute error (difference between direct and indirect evidence in log scale) is 0.228 and the variance of the error is 0.059. Using the normal approximation the obtained p-value is 0.35, demonstrating no evidence of inconsistency in the loop.

Table 16 Overall survival - Indirect and direct evidence for the closed loop using the Bucher method in the inspection of consistency

Contrast	Bucher method – Fixed effects		Bucher method – Random Effects		NMA fixed effects results 1/AFT (95% Cr Int)
	Direct 1/AFT (95% CI)	Indirect 1/AFT (95% CI)	Direct 1/AFT (95% CI)	Indirect 1/AFT (95% CI)	
DB vs DTIC	0.87(0.62,1.22)	0.69(0.5,0.96)	0.87(0.62,1.22)	0.69(0.5,0.96)	0.77 (0.61, 0.98)
DB.TM2mg vs DB	0.74(0.61,0.91)	0.59(0.38,0.91)	0.74(0.61,0.91)	0.59(0.38,0.91)	0.71 (0.60, 0.85)
DB.TM2mg vs VM	0.8(0.67,0.95)	1.00(0.64,1.55)	0.8(0.67,0.95)	1.00(0.64,1.55)	0.82 (0.70, 0.97)
VM vs DTIC	0.65(0.53,0.79)	0.81(0.53,1.25)	0.65(0.53,0.79)	0.81(0.53,1.25)	0.67 (0.56, 0.81)

Abbreviations: AFT, accelerated time failure; CI, Confidence interval; Cr Int, credible interval; DB, dabrafenib; DB.TM2mg, dabrafenib plus trametinib 2mg; DTIC, dacarbazine; VM, Vemurafenib

For PFS results the estimated variance of the random effects is 0.04 increasing the credible interval of random effects estimate of the direct evidence in the contrast DB.TM2mg vs DB,

and the credible intervals of the remaining constrast estimates in the indirect evidence. To test the null hypothesis of no inconsistency the estimated absolute error (difference between direct and indirect evidence in log scale) is 0.141 for fixed effects and 0.116 for random effects, respective variances of the error are 0.036 and 0.057. Using the normal approximation the obtained p-values are 0.46 and 0.63 respectively, demonstrating no evidence of inconsistency in the loop using both fixed and random effects.

Table 17 Progression free survival - Indirect and direct evidence for the closed loop using the Bucher method in the inspection of consistency

Contrast	Bucher method – Fixed effects		Bucher method – Random Effects		NMA fixed effects results 1/AFT (95% Cr Int)
	Direct 1/AFT (95% CI)	Indirect 1/AFT (95% CI)	Direct 1/AFT (95% CI)	Indirect 1/AFT (95% CI)	
DB vs DTIC	0.36(0.28,0.46)	0.31(0.24,0.41)	0.36(0.28,0.46)	0.32(0.22,0.48)	0.34 (0.28, 0.41)
DB.TM2mg vs DB	0.65(0.54,0.77)	0.56(0.4,0.78)	0.63(0.45,0.88)	0.56(0.4,0.78)	0.63 (0.54, 0.73)
DB.TM2mg vs VM	0.64(0.55,0.75)	0.74(0.53,1.04)	0.64(0.55,0.75)	0.72(0.46,1.12)	0.66 (0.57, 0.76)
VM vs DTIC	0.31(0.27,0.36)	0.36(0.26,0.51)	0.31(0.27,0.36)	0.35(0.23,0.55)	0.32 (0.28, 0.37)

Abbreviations: AFT, accelerated time failure; CI, Confidence interval; Cr Int, credible interval; DB, dabrafenib; DB.TM2mg, dabrafenib plus trametinib 2mg; DTIC, dacarbazine; VM, Vemurafenib

A9. What was the rationale for only including studies of patients who are treatment naive when presenting with metastatic disease in the NMA? (As stated in CS, Table 19).

Criteria for selection of the coBRIM study population required patients to be naïve to treatment for unresectable or metastatic disease (i.e., no prior systemic anti-cancer therapy for advanced disease; Stage IIIc and IV). In order to ensure study population consistency within the NMA, the search criteria were restricted to match the population of the primary evidence for the technology under appraisal (the coBRIM study).

The systematic review applied a comprehensive search strategy to identify studies reporting on first- or second-line treated metastatic melanoma patient populations, to ensure all potentially relevant studies were identified. Studies enrolling patients who had received prior treatment for an earlier stage of the disease, but who were treatment naïve when presenting with metastatic disease, were eligible for inclusion. A single study meeting this criteria was identified (Wolchok et al, 2010) reporting outcomes based on patients receiving second-line treatment but was excluded from the evidence networks to ensure comparable treatment naïve patient populations.

A10. In section 4.14 of the CS, it is stated that there are no additional ongoing studies (page 96). Were searches for ongoing studies conducted? If so please provide details of the search sources and dates.

A search was conducted on April 7th 2015 to identify any ongoing studies investigating cobimetinib in combination with vemurafenib, in metastatic melanoma. The following sources were searched to identify ongoing studies which met the PICOS criteria. This search did not identify any studies expected to report results within the following 12 months.

Search sources:

Clinical Trial gov: https://clinicaltrials.gov, European Union Clinical Trials Register: https://www.clinicaltrialsregister.eu, WHO Trials Registry: www.who.int/ictrp, British Association of Dermatologists guidelines: http://www.bad.org.uk, Scottish Intercollegiate Guidelines Network (SIGN): www.sign.ac.uk, Mapi Institute: http://www.proqolid.org/, INAHTA: http://www.inahta.org

A11. Please report the sources used for hand searching in the literature search for the NMA (CS, Figure 35).

The following sources were searched to supplement the electronic database searches:

1. Reference lists of included studies
2. The following websites:
    - Clinical Trial gov: https://clinicaltrials.gov
    - European Union Clinical Trials Register: https://www.clinicaltrialsregister.eu
    - WHO Trials Registry: www.who.int/ictrp
    - British Association of Dermatologists guidelines: http://www.bad.org.uk
    - Scottish Intercollegiate Guidelines Network (SIGN): www.sign.ac.uk
    - Mapi Institute: http://www.proqolid.org/
    - INAHTA: http://www.inahta.org

A12. Appendix 7 of the CS only provides Hazard Ratio (HR) and AFT values for OS, please could you provide equivalent values for PFS.

Resulting HR and AFT values for PFS from the indirect treatment comparison are provided in Table 18 below.

Table 18 HR and AFT calculated from IPD and published HR with 95% CI for PFS

Study	Treatment	Baseline Treatment	Published HR (95% CI)	HR (95% CI)	1/AFT (95% CI)
Flaherty et al, 2012a	Dabrafenib + trametinib 1mg	Dabrafenib	0.56 (0.37, 0.87)	0.55 (0.36, 0.84)	0.74 (0.56, 0.98)
	Dabrafenib + trametinib 2mg	Dabrafenib	0.39 (0.25, 0.62)	0.37 (0.23, 0.59)	0.54 (0.41, 0.71)
Flaherty et al, 2012b	Trametinib 2mg	Dacarbazine	0.45 (0.33, 0.63)	0.42 (0.31, 0.57)	0.46 (0.37, 0.58)
Hauschild et al, 2013 (BREAK-3)	Dabrafenib	Dacarbazine	NR	0.36 (0.25, 0.50)	0.36 (0.28, 0.46)
Larkin et al, 2014 (CoBRIM)	Vemurafenib	Vemurafenib + cobimetinib	1.96 (1.47, 2.56)	1.70 (1.36, 2.12)	1.59 (1.32, 1.90)
Long et al, 2015 (COMBI-d)	Dabrafenib + trametinib 2mg	Dabrafenib	0.67 (0.53, 0.84)	0.68 (0.54, 0.85)	0.72 (0.58, 0.90)
McArthur 2014 (BRIM-3)	Vemurafenib	Dacarbazine	0.38 (0.32, 0.46)	0.45 (0.38, 0.53)	0.31 (0.27, 0.36)
Robert et al,	Vemurafenib	Dabrafenib +	1.79	1.77	1.56

Study	Treatment	Baseline Treatment	Published HR (95% CI)	HR (95% CI)	1/AFT (95% CI)
2015		trametinib 2mg	(1.45, 2.17)	(1.44, 2.16)	(1.33, 1.82)

Abbreviations: AFT, accelerated failure time model; CI; confidence interval DB, dabrafenib; DB.TM1 mg, dabrafenib plus trametinib 1 mg; DB.TM2 mg, dabrafenib plus trametinib 2 mg; DTIC, dacarbazine; HR, hazard ratio; TM, trametinib; TMZ, temozolomide; TMZ.IFN, temozolomide plus interferon; VM, vemurafenib; VM.Cobi, vemurafenib plus cobimetinib

Section B: Clarification on cost-effectiveness data

B1. Please clarify how the health state costs for PFS and Progressed Disease (PD) of £378/month were derived.

To ensure consistency with prior Single Technology Appraisals in metastatic melanoma, the health state costs were taken from the ipilimumab NICE appraisal (TA268, December 2014, page 136 manufacturer submission) and vemurafenib NICE appraisal (TA269, December 2012, page 210 manufacturer submission). This cost is also consistent with the resource use costs for year 1 of treatment from the recent Nivolumab NICE appraisal, at £89.74 per week, equating to £389 per month. (TA384, Feb 2016 page 203 of manufacturer submission)

B2. **Priority question: Please provide more details of the EQ-5D utility values in the co-BRIM trial. Please provide the number of observations and mean utility scores at each time point, including baseline, for the patients for both arms, and for each category (PFS cobimetinib + vemurafenib; PFS vemurafenib; PD cobimetinib + vemurafenib; PD vemurafenib)**.

EQ-5D-5L data were collected during the coBRIM study. Utilities were calculated using the crosswalk method from EQ-5D-3L to EQ-5D-5L. Number of observations, mean utilities with standard deviation and 95% upper and lower values, and median values at each cycle are presented in Table 19 below

Utility over treatment cycle for each arm of the study are shown graphically in Figure 6.

Figure 6 Utility over treatment cycle in coBRIM

Figure 6 above marked as academic in confidence

Table 19 Utilities based on EQ5D5L values by visit – Crosswalk from EQ5D3L

Table 19 above marked as academic in confidence

B3. **The mean time on treatment reported in Table 40 of the CS (9.9 months) for vemurafenib differs from the value used in the economic model (11.3 months). Please clarify which is the correct value**.

This discrepancy between the CS and economic model is due to a typographical error within Table 40 of the CS. The mean time on treatment for vemurafenib monotherapy from the coBRIM study is 11.3 months.

B4. **Please provide details of the patient characteristics of those in the SEER (Surveillance, Epidemiology, and End Results) database referred to in CS page 108**.

Data on patients with malignant melanoma diagnosed between 1988 and 2007, with survival data available up to 2012, whose invasive melanoma was their first and only cancer diagnosis and in stage IV melanoma were extracted from the surveillance, epidemiology, and end results (SEER) database.

Patient characteristics (as down loaded June 2, 2015), are presented in Table 20 below.

Table 20 Demographics from surveillance, epidemiology, and end results (SEER) data 1973 - 2012

Variable		n (%)
Age at diagnosis group (years)	0-17	21 (0.4%)
	18-39	496 (10%)
	40-64	2224 (44.9%)
	65+	2214 (44.7%)
Age at diagnosis (years)	n	4955
	mean	60.6
	sd	16.3
	median	61
	Percentile 25th	49
	Percentile 75th	73
Gender	Male	3305 (66.7%)
	Female	1650 (33.3%)

R version 3.1.2 (2014-10-31)
Roche data on file: Source: / /opt/BIOSTAT/prod_ext3/cd66600a.pbe/m66601i.pbe / Demo_SEER_melanoma.R / Tue Mar 08 08:26 2016

B5. Please provide details on how the cure rate on page 109 of the CS has been calculated?

The cure rate on page 109 of the CS is based on data extracted from the SEER database and background mortality taken from US life tables. Likelihood estimation is used to find the maximum of the mixture of cure-rate methodology.

The likelihood uses the following expressions for the survival and the hazard functions. The survival at time t of a patient diagnosed at age a is given by:

$$S(t+a;\boldsymbol{\theta},\pi) \;= S^*(t+a)[\pi + (1-\pi)S_u(t;\boldsymbol{\theta})]$$

Where $S^*(t+a)$ is the background survival (based on background mortality from US life tables) and $S_u(t;\boldsymbol{\theta})$ is the survival of patients diagnosed with melanoma from SEER data.

Equivalently, the hazard function is given by the following expression:

$$h(t+a;\boldsymbol{\theta},\pi) \;= h^*(t+a) + \frac{(1-\pi)f_u(t;\boldsymbol{\theta})}{\pi + (1-\pi)S_u(t;\boldsymbol{\theta})}$$

The hazard function has two components. The first: $h^*(t+a)$ is attributed to background mortality, the second is the disease specific hazard from the SEER database. The latter includes: i) the 'cure fraction' π, ii) the density function $f_u(t;\boldsymbol{\theta})$ and iii) the survival function $S_u(t;\boldsymbol{\theta})$ for patients diagnosed with melanoma from the SEER database.

For the disease specific hazard the following parametric functions were considered: exponential, Weibull, log-logistic, log-normal, Gompertz, gamma and generalized gamma, each model leading to a different estimation of the 'cure fraction'.

Based on the information criteria AIC and BIC as well as on the goodness of fit plots, the model that best fits was the [redacted]

[redacted]

B6. Please provide AIC / BIC values for the parametric curves for time on treatment, CS page 126.

The parametric functions' goodness of fit for treatment duration were assessed using the AIC and BIC values, and the likelihood ratio between distributions. These values are provided for cobimetinib within the experimental arm in Table 21, vemurafenib within the experimental arm in Table 22 and vemurafenib within the comparator arm in Table 23.

Weibull and exponential distributions have the most favourable goodness of fit AIC and BIC values for both vemurafenib and cobimetinib in the experimental arm, with extremely close log-likelihood values between these distributions. The likelihood ratio test does not show significance between the distributions, therefore Weibull was chosen as the most conservative with respect to the resulting ICER.

Table 21 AIC and BIC values for parametric distributions of treatment duration for cobimetinib

	Log Likelihood	AIC	BIC	Likelihood-ratio test p-value
EXPONENTIAL	-367.3537	736.70746	740.21685	
WEIBULL	-367.3499	738.69973	745.7185	
LLOGISTIC	-369.1873	742.37469	749.39346	
LNORMAL	-371.6859	747.37188	754.39065	
GAMMA	-367.2787	740.55748	751.08564	

GOMPERTZ	-367.3537	738.70746	745.72624	
NPHWEIBULL	-367.3499	738.69973	745.7185	
WEIBULL vs EXPONENTIAL				0.9299
GAMMA vs WEIBULL				0.7061
GAMMA vs LNORMAL				0.003

Table 22 AIC and BIC values for parametric distributions of treatment duration for vemurafenib within experimental arm

	Log Likelihood	AIC	BIC	**Likelihood-ratio test p-value**
EXPONENTIAL	-352.3349	706.66977	710.17916	
WEIBULL	-351.764	707.52794	714.54672	
LLOGISTIC	-352.4619	708.92383	715.9426	
LNORMAL	-355.2753	714.55069	721.56947	
GAMMA	-351.4701	708.94016	719.46832	
GOMPERTZ	-352.2304	708.4608	715.47957	
NPHWEIBULL	-351.764	707.52794	714.54672	
WEIBULL vs EXPONENTIAL				0.2853
GAMMA vs WEIBULL				0.4433
GAMMA vs LNORMAL				0.0058

Table 23 AIC and BIC values for parametric distrubitions of treatment duration for vemurafenib within comparator arm

	Log Likelihood	**AIC**	**BIC**	**Likelihood-ratio test p-value**
EXPONENTIAL	-342.9552	687.91039	691.41572	
WEIBULL	-337.7361	679.4721	686.48276	
LLOGISTIC	-324.9784	653.95682	660.96748	
LNORMAL	-327.9093	659.81857	666.82923	
GAMMA	-327.7088	661.41754	671.93353	
GOMPERTZ	-342.8913	689.78262	696.79328	
NPHWEIBULL	-337.7361	679.4721	686.48276	
WEIBULL vs EXPONENTIAL				0.0012
GAMMA vs WEIBULL				<0.0001
GAMMA vs LNORMAL				0.5266

Section C: Textual clarifications and additional points

Please clarify what the '†' symbols mean in Figure 11, adjacent to the BRIM-3, COMBI-d and BREAK-3 trials.

The '†' symbol should include the follow explanation: '*Trial names with more than one publication contributing data for the same trial*'

References:

Bexelius C, Quigley J, Thuresson P-O, Hawkins N. The Comparative Efficacy of First-Line Treatments for Stage IIIC and Stage IV Melanoma: Results of a Systematic Review and Network Meta-Analysis. European Society for Medical Oncology (ESMO) congress 2014 - Poster presentation 1095P

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Flaherty K, Robert C, Hersey P et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367:107-14. (b)

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Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010 Feb;11(2):155-64.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name [redacted] **submitting on behalf of:**

Name of your organisation: NCRI/RCP/Melanoma Focus

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

What is the expected place of the technology in current practice?

Replacement for BRAF inhibitor monotherapy

How is the condition currently treated in the NHS?

See below

Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be?

There is no significant geographical variation, or difference in opinion regarding the clinical management between treating health care professionals in the UK.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Choice of first-line treatment for advanced melanoma is dictated by whether the tumour harbours an activating BRAF mutation, patient performance status, sites of disease and speed of disease progression. First-line treatment options presently include a BRAF inhibitor (vemurafenib or dabrafenib) or the anti-CTLA4 agent ipilimumab. The anti-PD1 agent pembrolizumab is approved post ipilimumab and BRAF inhibitor, the latter if appropriate.

BRAF inhibitors as single agents have response rates of approximately 50% and moderate toxicity, and are associated with a median progression free survival of around 7 months. Ipilimumab has low response rate (15-20%) but for those who benefit there can be durable response lasting some years, which translates to an overall survival advantage in comparison with cytotoxic chemotherapy in phase 3 trials. Toxicity is manageable in experienced hands. Pembrolizumab has a response rate of 30-40% and superior progression free and overall survival in comparison with ipilimumab in a phase 3 trial.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Tumours with activating BRAF mutations represent a distinct subgroup of around 40% of advanced melanomas.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

Advanced melanoma is treated at tertiary care oncology centres by specialist oncologists.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

No

If the technology is already available, is there variation in how it is being used in the NHS?

No

Is it always used within its licensed indications?

Yes

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

This combination of drugs is not covered in any national melanoma guidelines

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Little difference from vemurafenib given alone.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Patients will discontinue upon radiological disease progression. Repeat imaging will therefore be necessary throughout the duration of treatment, at clinically appropriate intervals.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

The trial data is appropriate and reflects anticipated UK clinical practice.

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

In the coBRIM trial (Larkin NEJM 2014) vemurafenib and cobimetinib combined were significantly superior to vemurafenib alone in terms of response rate and progression free survival. The trial is not yet mature for overall survival analysis.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Very similar to vemurafenib alone. There is an improvement in some skin side effects (keratotic skin lesions and squamous cell carcinomas). The marginally greater incidence of diarrhoea, cardiac dysfunction and visual disturbance compared with vemurafenib alone does not represent significant management problems for clinicians and these events do not result in hospitalisation of patients.

In the coBRIM trial the rate of G3 reduction in LVEF was the same in both arms (1%) and ECHO monitoring would only be done in routine practice in patients with pre-existing cardiac problems, which is relatively rare in advanced melanoma. The majority of ocular toxicity observed in coBRIM was of low severity grade and was managed with dose modification of cobimetinib. Surveillance ophthalmic examination identified mostly asymptomatic low severity grade serous retinopathy, for which clinical significance is uncertain (De La Cruz-Merino ASCO 2015 Abstract 9033).

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

N/A

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE

technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

No issues identified

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The only significant costs will be in pharmacies and the fact that patients remain on combination treatment longer than single agent BRAF inhibitor treatment because of increased duration of benefit.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. 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;

No

- 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;

No

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

No

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Not applicable

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

[ICobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]~~ong form title~~]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **[Melanoma Focus~~insert name of nominating organisation~~]** and consequently I will not be submitting a personal statement.

Name: .....

Signed: .....

Date: 9/5/16

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Melanoma UK Melanoma??UKMelanoma UK Melanoma UK Melanoma??UK

Your position in the organisation: Volunteer VolunteerVolunteer Volunteer Volunteer

Brief description of the organisation: Charity / Support Group Charity????Support??GroupCharity / Support Group Charity????Support??Group Charity / Support Group

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

It??varies??according??to??the??stage??of??the??disease It varies according to the stage of the disease.It varies according to the stage of the disease. It??varies??according??to??the??stage??of??the??disease It varies according to the stage of the disease.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Ideally??a??cure??if??not??then??stable??diseaseIdeally a cure, if not then stable disease Ideally a cure, if not then stable disease.. Ideally??a??cure??if??not??then??stable??disease Ideally a cure, if not then stable disease.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Care??id??generally??very??good??However??treatments??only??work??for??some??patients??and??then??sometimes??not??for??long Care id generally very good. However, treatments only work for some patients and then sometimes, not for long.Care id generally very good. However, treatments only work for some patients and then sometimes, not for long. Care??id??generally??very??good??However??treatments??only??work??for??some??patients??and??then??sometimes??not??for??long Care??id??generally??very??good??However??treatments??only??work??for??some??patients??and??then??sometimes??not??for??long

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Assing a MEK inhibitor to the BRAF inhibitor, extends the period before the melanoma becomes resistant to the treatment. This extends life.

Assing??a??MEK??inhibitor??to??the??BRAF??inhibitor??extends??the??period??before??the??melanoma??becomes??resistant??to??the??treatment??This??extends??lifeA Assing a MEK inhibitor to the BRAF inhibitor, extends the period before the melanoma becomes resistant to the treatment. This extends life.ssing a MEK inhibitor to the BRAF inhibitor,

extends the period before the melanoma becomes resistant to the treatment. This extends

life. Assing??a??MEK??inhibitor??to??the??BRAF??inhibitor??extends ??the??period??before??the??melanoma??becomes??resistant??to??the??treatment??This??extends??life Assing a MEK inhibitor to the BRAF inhibitor, extends the period before the melanoma becomes resistant to the treatment. This extends life.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

This??treatment??would??be??very??good??for??patients??with????ahigh??tumour??loas??and??aggressive??disease??It??was??a??high??response??rate??with??manageable??side??effects This treatment would be very good for patients with ahigh tumour loas and aggressive disease. It was a high response rate with manageable side effects.This treatment would be very good for patients with ahigh tumour loas and aggressive disease. It was a high response rate with manageable side effects. This??treatment??would??be??very??good??for??patients??with????ahigh??tumour??loas??and??aggressive??disease??It??was??a??high??response??rate??with??manageable??side??effects This treatment would be very good for patients with ahigh tumour loas and aggressive disease. It was a high response rate with manageable side effects.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Please list any concerns patients or carers have about the treatment being appraised.

side??effects side??effectsside effects side effects side??effects

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment

as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Current monotherapy with vemurafinib less effective than combo being appraised.

  Current??monotherapy??with??vemurafinib??less??effective??than ??combo??being??appraisedCurrent monotherapy with vemurafi Current monotherapy with vemurafinib less effective than combo being appraised.nib less effective than combo being appraised. Current??monotherapy??with??vemurafinib??less??effect ive??than??combo??being??appraised Current monotherapy with vemurafinib less effective than combo being appraised.
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  patients The??more??effective??treatments??available??the??better??for??patients
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CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Declared competing interests of the authors

None

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Rider on responsibility for report

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

This report should be referenced as follows:

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Contributions of authors

Keith Cooper (Senior Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. Petra Harris (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report. Geoff Frampton (Senior Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report. Christian Boehler (Independent

Consultant) critically appraised the economic evaluation and drafted the report. Jonathan Shepherd (Principal Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor.

Word count: 33,461

Commercial in confidence (CIC) information in blue
Academic in confidence (AIC) information in yellow

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LIST OF ABBREVIATIONS

AE	Adverse events
AFT	Accelerated failure time
AIC	Academic in confidence
AkIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CI	Confidence interval
CIC	Commercial in confidence
Cob	Cobimetinib
CR	Complete response
CRL	Credible interval
CS	Company's submission
CSR	Clinical study report
DOR	Duration of response
DIC	Deviance Information Criterion
DTIC	Dacarbazine
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	EuroQoL five dimension questionnaire
ERG	Evidence Review Group
HRQoL	Health-related quality of life
HR	Hazard ratio
HRG	Healthcare Resource Groups
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein kinase
MEK	MAP extracellular signal-regulated kinases
mITT	Modified Intention-to-Treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PFS	Progression-free survival
PH	Proportional hazards
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SG	Standard Gamble

STA	Single Technology Appraisal
SmPC	Summary of product characteristics
TOT	Time on Treatment
TTO	Time Trade Off
Vem	Vemurafenib

SUMMARY

Scope of the company submission

The company's submission (CS) generally reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). The scope was to consider adults with unresectable or metastatic BRAF V600 mutation-positive melanoma. The CS considers the same patient population, but due to evidence limitations was restricted to a treatment-naïve adult population with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. The CS therefore does not consider patients previously treated for advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. Expert advice to the ERG is that many BRAF mutation positive patients (up to 70%) would be treated with immunotherapy first line before switching to BRAF inhibitor and MEK (MAP extracellular signal-regulated kinases) inhibitor treatment as necessary. However, there are no data available to suggest that outcomes would be worse for second line treatment.

Summary of submitted clinical effectiveness evidence

Overall, the literature searches conducted by the company were appropriate, comprehensive and well designed, although searches for the network meta-analysis (NMA) were approximately a year out of date. The ERG update of the searches for the NMA did not identify any potentially additional relevant studies. Similarly, updating searches for the clinical-effectiveness review for the last six months also revealed no additional relevant studies.

The CS presents evidence of the clinical effectiveness of the MEK inhibitor cobimetinib in combination with the BRAF inhibitor vemurafenib based on one multi-centre, phase III randomised controlled trial (RCT), the coBRIM trial. The RCT compared the combination of vemurafenib (960 mg orally twice daily for a 28-day cycle) plus cobimetinib (60 mg orally once daily for 21 days, followed by 7 days off) against vemurafenib (960 mg orally twice daily) plus placebo in patients with previously untreated unresectable locally advanced or metastatic BRAF V600 mutation–positive melanoma.

The coBRIM trial was considered by the ERG to be of reasonable methodological quality; however, there was a lack of clarity in the reporting of the randomisation and allocation concealment procedures which meant the risk of selection bias is uncertain. There were also

imbalances in discontinuations ‘for any reason’ between the randomised treatment groups (discontinued both vemurafenib + placebo: n=138; discontinued both vemurafenib + cobimetinib arm: n=102), indicating possible attrition bias. The company suggests that the imbalances in discontinuations between the groups were not unexpected, given that the cobimetinib was anticipated to extend survival.

Results of the coBRIM trial

Results were presented in the CS for various data cutoff time points. The primary end point of investigator-assessed progression-free survival (PFS) was defined as the time from randomisation to either the first occurrence of disease progression as assessed by the investigator according to response evaluation criteria in solid tumours (RECIST) 1.1 criteria, or death from any cause. The median PFS was 9.9 months in the vemurafenib + cobimetinib group and 6.2 months in the vemurafenib + placebo group, with a hazard ratio (HR) for death or disease progression of 0.51 (95% Confidence interval (CI), 0.39 to 0.68; primary investigator analysis, data cutoff 9th May 2014).

The median duration of overall survival (OS), defined as the time from randomisation to death from any cause, was 22.3 months in the vemurafenib + cobimetinib group and 17.4 months in the vemurafenib + placebo group, with a HR for death of 0.70 (95% CI, 0.55 to 0.90; final analysis, data cutoff 28th August 2015).

The proportion of patients with complete response (cobimetinib 10% vs 4% placebo) and partial response (cobimetinib 57% vs 40% placebo) favoured the vemurafenib + cobimetinib group (planned analysis, data cutoff 9th May 2014).

Limited results were reported for health-related quality of life (HRQoL) based on the EuroQoL Five Dimension Questionnaire (EQ-5D) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) instrument. Overall, there appears to be some (non-statistically significant) pre-progression HRQoL benefit associated with vemurafenib + cobimetinib compared to vemurafenib + placebo. It is unclear whether the slightly higher HRQoL estimates in the vemurafenib + cobimetinib arm reflect HRQoL improvements resulting from less insomnia and/or other factors (e.g. the incidence of non-melanoma skin cancers which was lower in the vemurafenib + cobimetinib arm).

The most common adverse events (AE) for those treated with vemurafenib + cobimetinib (experienced by at least 20% of patients in either of the study group) included diarrhoea, photosensitivity, serous retinopathy, nausea and vomiting, elevated levels of creatine phosphokinase and aspartate aminotransferase. None of the observed differences between groups were tested statistically. Grade 4 AEs appeared to be more common in the vemurafenib + cobimetinib group (13% vs 9% placebo).

[redacted] An additional safety analysis will be conducted following the analysis for final OS, [redacted]

[redacted]

Results of the NMA

The NMA allowed a comparison between vemurafenib + cobimetinib combination therapy against dabrafenib monotherapy. The NMA used an accelerated failure time (AFT) model with outcomes for PFS and OS. The evidence network was sparse, with only one trial informing each comparison. Clinical heterogeneity between the trials in the network was not discussed. Results from the NMA were more favourable to the vemurafenib + cobimetinib combination therapy on measures of survival compared to treatment with dabrafenib monotherapy.

Summary of submitted cost effectiveness evidence

A systematic search of the literature was conducted by the company to identify economic evaluations of cobimetinib in combination with vemurafenib compared to any other BRAF inhibitor for advanced BRAF V600 mutation-positive melanoma. The review did not identify any relevant studies.

The company's de novo cost effectiveness analysis used a partitioned survival model to estimate the cost-effectiveness of cobimetinib in combination with vemurafenib compared against vemurafenib and against dabrafenib. The model adopted a time horizon of 30 years and

a cycle length of one week. The model consisted of three health states: progression-free survival, progressed disease and death. As recommended by NICE, a discount rate of 3.5% was used for both costs and health outcomes.

The economic evaluation used data from the coBRIM trial for the comparison between vemurafenib + cobimetinib against vemurafenib, and the NMA for the indirect comparison of vemurafenib + cobimetinib against dabrafenib. Health related quality of life utility values were calculated from data collected from the coBRIM trial, but these data were predominately for patients whose disease had not yet progressed. Utility values for progressed disease was used from a separate published study.

Results of the economic model were presented as the incremental cost per quality adjusted life year (QALY) and the incremental cost per life years gained. Two of the comparators (vemurafenib and dabrafenib) have a confidential patient access scheme (PAS) in place. Results were presented in the CS at the drug list price and at estimated discounted PAS prices. The results of the cost effectiveness analyses at list prices showed an incremental cost effectiveness ratio (ICER) for vemurafenib + cobimetinib of £150,514 per QALY compared to vemurafenib, and £209,942 compared to dabrafenib.

The company performed a range of deterministic and probabilistic sensitivity analyses to assess model uncertainty. The ICER remained above £50,000 per QALY in all sensitivity and scenario analyses, including when the cost of cobimetinib was reduced to zero. The probabilistic sensitivity analysis (PSA) estimated a 0% probability that vemurafenib + cobimetinib is cost effective at a willingness to pay threshold of £50,000 per QALY gained.

Commentary on the robustness of submitted evidence

Strengths

The company's systematic review of clinical effectiveness followed standard procedures and is of good quality. The ERG is not aware of any additional relevant published trials that could be included.

The key RCT, coBRIM, is generally well-designed and provides an appropriate evidence base to inform the assessment of clinical and cost-effectiveness in this appraisal.

In the absence of head-to-head direct evidence the NMA enabled indirect comparisons to be made between vemurafenib + cobimetinib against dabrafenib monotherapy.

The structure of the economic model was appropriate, comprehensive and reflected the clinical pathway for patients with advanced melanoma. The model was well-structured and consistent with the outcomes from the coBRIM trial.

The methods chosen for the analysis were generally appropriate and conformed to NICE methodological guidelines.

The company performed a wide range of sensitivity analyses including one-way, probabilistic and scenario analyses to assess model uncertainty.

Weaknesses and areas of uncertainty

The quality assessment of the coBRIM trial pointed to some areas of uncertainties based on randomisation and allocation concealment procedures, and a potential risk of attrition bias favouring the vemurafenib + cobimetinib treatment group.

The evidence network of the NMA was sparse, with only one trial informing each comparison, and there was no discussion of clinical heterogeneity between the trials in the network.

The two comparator treatments have not been compared in a fully incremental analysis. Rather, two separate analyses with different assumptions have been conducted that compare vemurafenib + cobimetinib against vemurafenib and against dabrafenib. These analyses use different assumptions and so it is not possible to integrate the two analyses into a fully incremental analysis.

The model results are sensitive to the parametric curves chosen to extrapolate beyond the coBRIM trial data for PFS, OS and time on treatment. Other parametric curves may also provide plausible extrapolation and these result in less favourable ICERs for vemurafenib + cobimetinib.

Furthermore, the ERG considered that a more reasonable approach to estimating the time on treatment was to use the Kaplan-Meier data with a loglogistic tail.

There is inconsistency in the dosing assumptions used in the comparison between vemurafenib + cobimetinib against dabrafenib. For vemurafenib + cobimetinib the actual dose is used and for dabrafenib the planned dose is used. However the actual dose of vemurafenib + cobimetinib, and hence the estimated cost of the intervention was lower than the planned dose in the coBRIM trial, which in turn made the intervention appear more favourable when compared to dabrafenib.

Summary of additional work undertaken by the ERG

The ERG conducted the following scenario analyses:

i) Cure rate fraction removed
ii) Time to treatment (TOT) extrapolation curve changed to Kaplan-Meier (KM) with log-logistic tail
iii) Changes to utility values
iv) Consistency in dosing between vemurafenib + cobimetinib and dabrafenib
v) Shorter treatment duration
vi) Inclusion of subsequent treatment costs
vii) Assuming equal efficacy between vemurafenib and dabrafenib for OS
viii) Combination analysis (scenario ii, iii and iv)

The results shown in this report are based on the drug list prices. The analyses have also been repeated in a separate confidential appendix for the NICE Appraisal Committee using the PAS drug discount prices for vemurafenib and for dabrafenib. Of these scenarios, the two with the largest impact on the model results were changing the parametric curve used for TOT (scenario ii) which increased the ICER to £204,340 per QALY for vemurafenib + cobimetinib compared against vemurafenib; and reducing the dosage for dabrafenib (scenario iv) which increased the ICER to £223,277 per QALY for vemurafenib + cobimetinib compared against dabrafenib. The ERG's preferred base case compared vemurafenib + cobimetinib to vemurafenib and dabrafenib with results presented as an incremental analysis. The preferred base case included changes to the TOT extrapolation curve (scenario ii), changes to the utility values for the progressed disease health state (scenario iii) and changes to the dosing for dabrafenib

(scenario iv). With these changes the ICER for vemurafenib + cobimetinib compared to vemurafenib is £223,738 per QALY gained. In summary, all of the additional sensitivity and scenario analyses conducted by the ERG resulted in ICERs above £100,000 per QALY gained.

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to NICE from Roche on the clinical effectiveness and cost effectiveness of cobimetinib (brand name: Cotellic) in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarifications on some aspects of the CS were requested from the manufacturer by the ERG via NICE on 1st March 2016. A response from the company via NICE was received by the ERG on 16th March 2016 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of the company's description of the underlying health problem

The description of melanoma appears to be appropriate and the CS outlined the different forms and its natural history. Early stages of melanoma (stage I or II), in which the cancer has not spread, are generally asymptomatic and can often be cured by surgery (resection). Tumour spread can occur, either to nearby lymph nodes (stage III) or other parts of the body (stage IV) and a mutated form of the BRAF gene (called BRAF V600) is found in about half of melanomas. The mutated gene means that the cells produce too much BRAF protein, leading to uncontrolled cell division and growth of the tumour.

The NICE guidance (NG14)[1] for assessment and management of melanoma published in 2015 report 13,348 new cases of melanoma in 2011, with 2209 related deaths. At diagnosis, around 1% of melanomas are stage IV. The guidance states melanoma is the second most common cancer in adults aged between 25 and 49, with more than 900 adults under the age of 35 diagnosed each year in the UK. This means that melanoma leads to more years of life lost than many more common cancers,[1] and the incidence of malignant melanoma is reported to be increasing every year.[2]

2.2 Critique of the company's overview of current service provision

The CS provides a detailed list of existing NICE guidelines, pathways and technology appraisals relevant to this appraisal (CS Section 3.5, page 35). Figure 1 (CS page 33) illustrates the NICE stage IV melanoma treatment pathway.

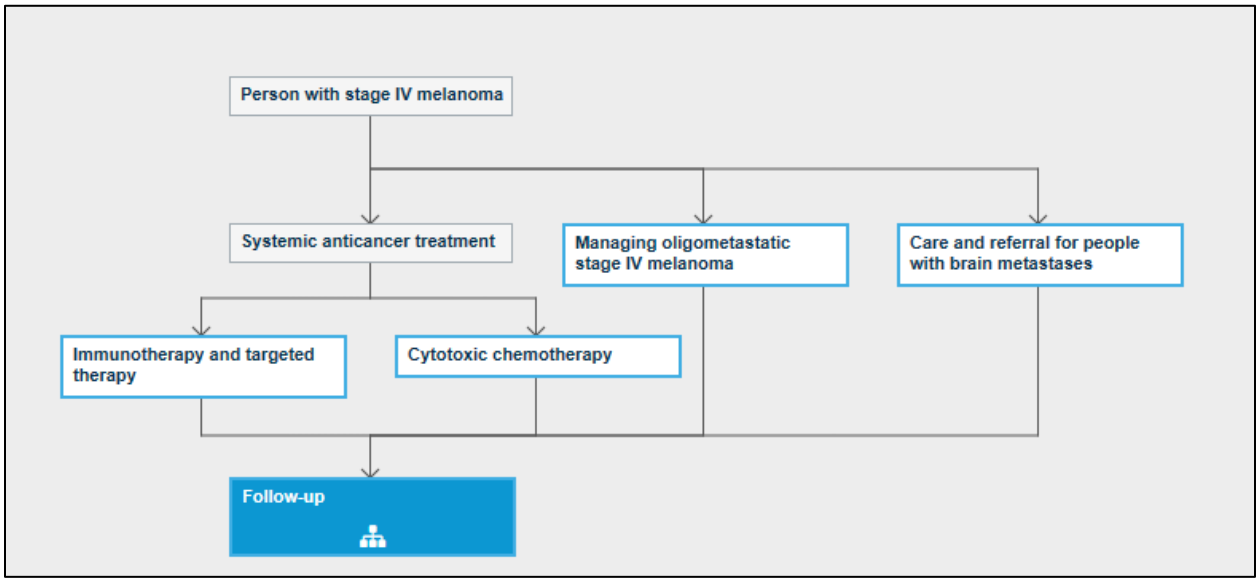


Figure 1 NICE Melanoma Pathway for the management of stage IV melanoma (2016)[3]

NICE has recommended immunotherapy and targeted therapy, and chemotherapy treatment for the treatment of stage IV melanoma (line 3 in Figure 1). These include nivolumab,[4] ipilimumab,[5, 6] dabrafenib,[7] vemurafenib,[8] and pembrolizumab[9,10] (Table 1) each varying in their marketing authorisation and some dependant on a patient access scheme (PAS). NICE clinical guidelines recommend dacarbazine for people with stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable.[1] Nivolumab or pembrolizumab are said to be used in about 60 - 70% of BRAF mutation positive patients according to clinical advice to the ERG, with a preference for pembrolizumab to nivolumab due to a shorter treatment cycle.

Certain drugs selectively target the BRAF enzyme, inhibiting its action and the mitogen-activated protein kinase (MAPK) pathway, which is a signalling pathway important for cell growth, proliferation, and survival. Cobimetinib is an antineoplastic agent targeting the MEK enzyme in the MAPK pathway. It inhibits the action of the abnormal BRAF protein, with the aim of slowing the growth and spread of the cancer.

Table 1 NICE approved therapies for the treatment of stage IV melanoma

Drugs	NICE guidance – drug recommended for:
Immunotherapy	
Ipilimumab	Previously treated advanced (unresectable or metastatic) melanoma (NICE TA 268); Previously untreated advanced (unresectable or metastatic) melanoma (NICE TA319)
Nivolumab	Advanced (unresectable or metastatic) melanoma (NICE TA384)
Pembrolizumab	Disease has progressed following ipilimumab and, if BRAF V600 mutation positive, also a BRAF inhibitor (NICE TA357); Advanced melanoma not previously treated with ipilimumab (NICE TA366)
Targeted therapy	
Dabrafenib	Unresectable or metastatic BRAF V600 mutation‑positive melanoma (NICE TA321)
Vemurafenib	Locally advanced or metastatic BRAF V600 mutation‑positive malignant melanoma (NICE TA269)
Cytotoxic chemotherapy drugs	
Dacarbazine	Stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable (NICE NG14)

Cobimetinib is licensed to be used in combination with the BRAF inhibitor vemurafenib. The rationale for combination therapy is stated in the CS to be to reduce the disease progression, following a period of tumour response, which is common with BRAF inhibition monotherapy. According to expert clinical advice provided to the ERG, 30 - 40% of BRAF mutation positive patients in clinical practice would potentially start with combination therapy.

2.3 Critique of company's definition of decision problem

Population

The patient population addressed in the CS is broadly similar to that specified in the NICE scope and for whom cobimetinib is licensed. The patient population specified in the scope is 'Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma. The CS includes the same patient population, but currently relevant comparative evidence exists only for treatment-naïve patients and hence the company presents clinical and cost effectiveness evidence to support the use of cobimetinib in combination with vemurafenib for treatment-naïve patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. In contrast to the description of current practice in the CS (which states that a BRAF inhibitor is the usual first-line treatment in this patient group), expert clinical advice to the ERG suggested that some patients (estimated up to 70%) with advanced (unresectable or metastatic) BRAF mutation positive melanoma would receive immunotherapy as first line treatment (e.g. ipilimumab, pembrolizumab, or nivolumab), before potentially switching to targeted BRAF mutation inhibitor therapy as necessary. A BRAF inhibitor might be a more commonly used first line treatment for BRAF mutation positive patients with a higher burden of disease or faster disease progression, given that the onset of action with certain immunotherapies may be relatively slow (e.g. around three months for ipilimumab). The submission, therefore, does not specifically cover patients with previous treatment experience. However, expert clinical opinion is that efficacy and safety of vemurafenib + cobimetinib in this group would be similar to that seen in treatment naïve patients.

Intervention

The intervention addressed in the CS reflects the NICE scope and the marketing authorisation. The recommended dose of cobimetinib is 60 mg (3 tablets of 20 mg each), taken orally once daily for 21 days, followed by a 7 day break (Days 22 to 28). The dose for vemurafenib is 960 mg taken orally twice daily (4 tablets of 240 mg, equivalent to a total daily dose of 1,920 mg of 8 tablets in total) taken without a break (days 1-28 of each cycle). For both drugs, down-dosing in response to toxicity is possible as deemed clinically appropriate and both are continued until disease progression. The CS suggests that the combination treatment should only be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products in specialist secondary, or tertiary care centres. As both drugs in the combination treatment are taken orally, it is stated that there is no impact on NHS staff in terms of administering the drugs. However, monitoring and dose adjustments due to AEs may be required and although it is suggested that this would not require additional NHS resources as this is established clinical practice in England and Wales for this type of treatment, this has not been established as yet.

Comparators

Two comparators are specified in the NICE scope: vemurafenib and dabrafenib, which are both used in treatment-naïve patients and those with prior treatment experience for malignant melanoma. Direct evidence was only available for the comparison with vemurafenib, from the pivotal coBRIM trial. However, comparative evidence for dabrafenib was provided in the form of an indirect comparison in the CS (see Section 3.1.7 of this report for a description and critique of the indirect comparison).

Outcomes

Clinical evidence in the CS is provided for all five outcomes specified in the NICE scope: progression-free survival (PFS), overall survival (OS), response rates (reported as objective response rate (ORR), best overall response (BORR) and duration of response), adverse effects (AEs) of treatment and health-related quality of life (HRQoL). These outcomes are widely used and accepted endpoints in oncology trials. Pharmacokinetic measures were also employed, but not included in the CS.

Economic analysis

As specified in the final NICE scope, the cost effectiveness of treatments were expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 30-year time horizon (deemed equivalent to a lifetime horizon for this patient population) and costs were considered from the perspective of NHS England.

Other relevant factors

Subgroups

No subgroups are specified in the NICE scope or the decision problem. As noted above, evidence in the CS was only available from treatment-naïve patients. The CS presents clinical effectiveness results from the coBRIM trial for 12 pre-specified subgroups (NB. cost effectiveness evidence is not presented for these sub-groups):

- Disease stage (IIIc, M1a, M1b, M1c)
- Disease stage (IIIc/M1a/M1b, M1c)
- Age (≤ 65 years, > 65 years) at randomisation

• Race (non-White, White)
• Sex (female, male)
• Geographic region (North America, Europe, Australia/New Zealand/others)
• Eastern Cooperative Oncology Group (ECOG) performance status at randomisation (0, 1)
• LDH (lactate dehydrogenase) (normal, elevated)
• Presence of brain metastases (yes, no)
• Time since metastatic disease diagnosis (< 6 months, ≥ 6 months)
• Prior adjuvant therapy (Yes, No)
• BRAF V600 mutation status (V600E, V600K)

Expert clinical advice to the ERG is that these subgroups are appropriate, with no further subgroups of clinical importance suggested.

Equity or equality issues
The CS states that it is not believed that the use of cobimetinib (in combination with vemurafenib) will be associated with any equality issues (CS Section 3.8, page 36) and the ERG concurs with this assessment.

Other valid issues
The CS points out that BRAF mutation testing is part of routine management for patients with advanced melanoma in the UK, therefore is not considered an additional cost or resource burden to the system (CS page 128). However, as per the prior vemurafenib technology appraisal (TA269),[8] a cost of £95 per test is incorporated into the model, which has no incremental effect as this cost is applied to both the intervention and all comparators. Clinical opinion provided to the ERG concurs with this approach.

There is currently no PAS in place for cobimetinib, though there is one for vemurafenib and for dabrafenib.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's approach to their systematic reviews

3.1.1 Description of the company's search strategies

The CS reports separate literature searches for the following systematic reviews:

- Clinical-effectiveness (searched to September 2015)
- Cost-effectiveness (searched to December 2015)
- Indirect treatment comparison (searched to April 2015)
- Measurement and valuation of health effects (searched to December 2015)
- Cost and resource use (searched to December 2015)

The search sources and strategies for each of these searches are reported in appendices to the CS. The ERG regards the searches to be comprehensive, well designed, explicitly documented and fit for purpose. The search terms have been documented line-by-line as applied to the databases, though for the clinical-effectiveness search the number of hits per line is not documented, which lessens transparency.

An appropriate range of databases were included in each search, including the core databases of MEDLINE (and MEDLINE In-Process), Embase and the Cochrane Library. Additional specialist databases were included as appropriate to certain reviews (e.g. Econlit was searched for the cost-effectiveness and the costs and resources search). Conference proceedings were searched for all the reviews, with the exception of the indirect treatment comparison. The conference proceedings were searched from 2013-2015 for all reviews except the clinical effectiveness review which was searched from 2014-2015. The conferences searched were appropriate to the scope of the appraisal, including key oncology conferences (American Society of Clinical Oncology; European Society for Medical Oncology), and melanoma-specific conferences (Society for Melanoma Research). The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conference was searched for the cost-effectiveness review, the measurement and valuation of health effects review and the cost and resource use review.

Some hand-searching took place, with reference lists of included studies reported for all searches. Additional sources were handsearched as appropriate to the review in question (e.g. the Research Papers in Economics (RePEc) resource was searched for the cost effectiveness review and the costs and resources review).

The searches were generally up to date, with the exception of the indirect treatment comparison search which was current only to April 2015. The ERG updated this search on MEDLINE and MEDLINE In-Process and Embase but did not identify any potentially relevant new studies (see

section 3.1.7). The clinical-effectiveness review was current to September 2015, and the ERG also updated the searches for this review covering the period 2015 to 2nd March 2015 on MEDLINE, MEDLINE In-Process and Embase. The results were screened by an ERG systematic reviewer and no additional relevant studies were identified.

The CS does not mention if searches were conducted to identify on-going studies. The company responded to a clarification question from the ERG (clarification response A10) that the following databases were searched on April 7th 2015: ClinicalTrials.gov; European Union Clinical Trials Register; World Health Organisation Trials Registry; British Association of Dermatologists guidelines; Scottish Intercollegiate Guidelines Network (SIGN): Mapi Institute; and the International Network of Agencies for Health Technology Assessment (INAHTA). In terms of the results of this search all that is stated is that it did not identify any studies expected to report results within the following 12 months. In advance of the company's response to the clarification question, the ERG conducted a separate search of the following trials databases Sources: UK Clinical Research Network Study Portfolio (UKCRN), ISRCTN, WHO International Clinical Trials Registry Platform; clinicaltrials.gov; and rochetrials.com. One potentially relevant trial was identified, discussed in Section 3.1.3.1.

The ERG also checked the ScHARRHUD (Health Utilities Database) database for studies reporting health utility papers appertaining to melanoma, however the only relevant result was already cited in the CS.

In summary, we consider that the searches conducted by the company to support the systematic reviews in the submission are generally comprehensive and are reported transparently. We updated two of the database searches but did not identify any additional relevant published studies.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The CS provides a clear overview of the inclusion and exclusion criteria (CS Table 6, page 38). The criteria appear to be in line with the marketing authorisation, the NICE scope, and the company's decision problem.

No limits were placed on inclusion relating to the quality of the RCTs, but only phase II, III or IV RCTs, or systematic reviews or meta-analyses of RCTs were eligible for inclusion. Setting was not an inclusion criterion. A PRISMA diagram, illustrating the numbers of references included and excluded at each stage of the systematic literature review conducted for the CS, is provided in Figure 2. The total number of records identified through database searching seems low (n=57), even after duplicate removal. However, as we are not aware of any relevant studies that were not identified in the company's systematic review, this does not necessarily indicate that their search strategy was flawed.

The company did not address any potential bias that may have arisen in relation to their searches or inclusion/exclusion criteria, but processes appear to have been robust.

3.1.3 Identified studies

The CS identified one relevant RCT (coBRIM).[12] The majority of the details of the RCT in the CS were summarised in tables such as trial design, intervention, population, patient numbers and statistical analysis. Trial outcome measures and subgroups were described in text.

References including the coBRIM trial[13-15] were provided electronically, as was the clinical study report (CSR). The coBRIM trial was sponsored by f. Hoffmann – La Roche/Genentech.

The company did not identify any non-randomised or non-controlled evidence relevant to the decision problem (CS Section 4.11). However, it appears from the CS that non-randomised studies were not searched for (an RCT filter was applied to the clinical effectiveness search strategies).

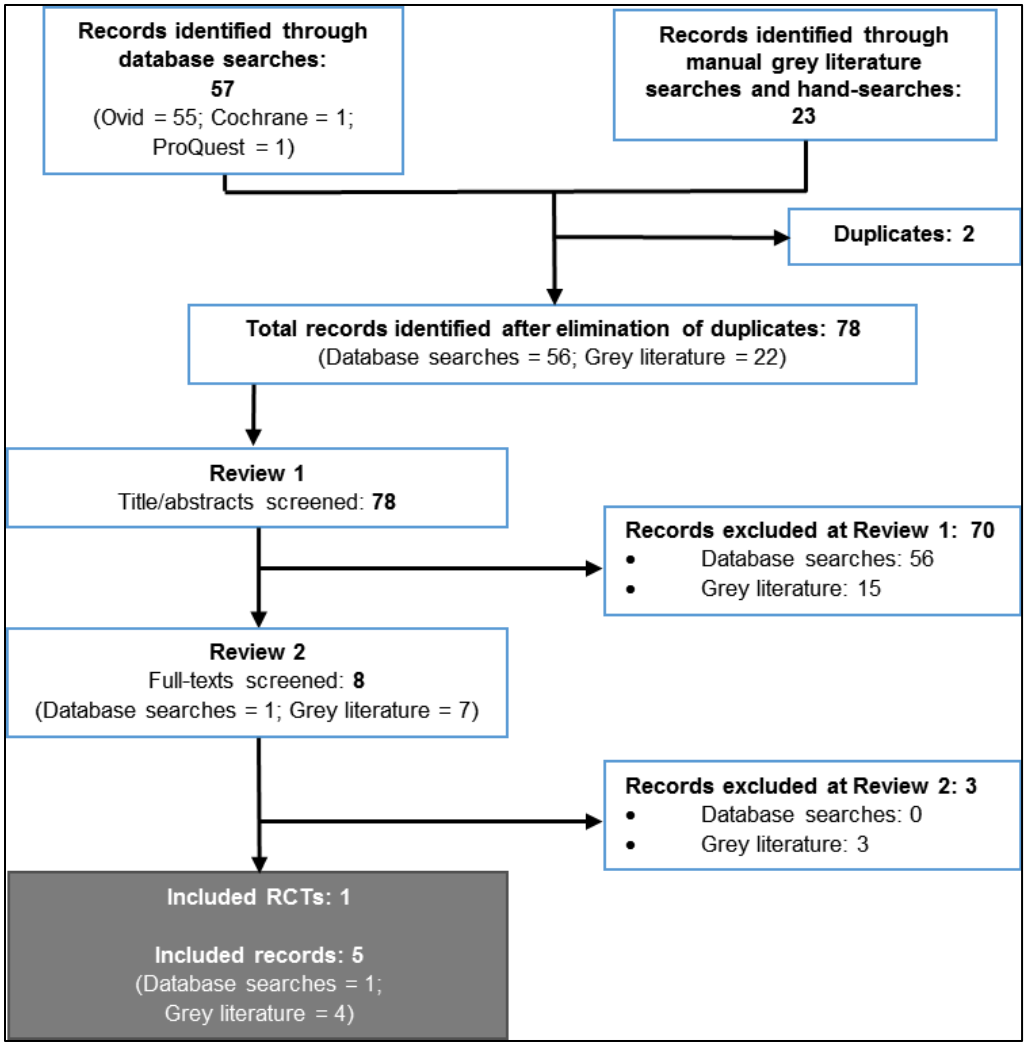


Figure 2 PRISMA diagram for systematic literature review of RCTs (search cut-off date: 8th or 9th September 2015; based on CS figure 2, page 40)

The trial journal publication[12] states that there were no significant differences in baseline characteristics between the study groups, but no p values were provided to support this. Both the trial publication[12] and the CS state that the characteristics of the patients at baseline were generally well balanced between the two study groups, with baseline characteristics provided in table format. Apart from ECOG performance-status score, the ERG would agree with this statement. While differences are said to not be statistically significant, 9% more participants in the intervention group were rated ECOG performance-status score 0 (defined as the patient is fully active and able to carry on all performance without restriction) and 9% fewer were rated ECOG performance-status score 1 (the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) than in the control group. Further, 3% fewer participants in the intervention group were assessed at baseline as

metastatic status M1c compared to the intervention group and 4% more participants were assessed as unresectable stage IIIC (i.e. less advanced metastases) (Table 2) than in the control group. However, while these small imbalances might be expected to favour the placebo group, expert advice to the ERG did not consider that these differences would influence the improvement in clinical outcomes for those treated with cobimetinib.

3.1.3.1 Ongoing trials

In their response to a clarification question from the ERG, the company stated that a search for ongoing trials did not identify any studies which were expected to report results within the following 12 months. A search for ongoing trials conducted by the ERG identified one trial of potential interest (summarised in Table 3). The trial is comparing two different regimens of combination therapy: one with a vemurafenib monotherapy induction period, and one with a cobimetinib monotherapy induction period. However, as there is no comparison between combination therapy and monotherapy this trial is not fully relevant to the scope of the appraisal.

Table 2 Overview of baseline characteristics in the coBRIM trial

Parameter (data based on CS Table 14 , page 59 – 60)	**CoBRIM trial**	
	Vemurafenib + cobimetinib	**Vemurafenib + placebo**
Sample size, n	n=247	n=248
Age, mean years (range)	56 (23-88)	55 (25-85)
Male sex, n (%)	146 (59)	140 (56)
White, n (%)[a]	227 (92)	235 (95)
Geographic region n (%)		
Australia, New Zealand, or Israel	40 (16)	38 (15)
Europe (including Russia and Turkey)	182 (74)	184 (74)
North America	25 (10)	26 (10)
ECOG performance-status score n (%)[b]		
0	184/243 (76)	164/244 (67)
1	58/243 (24)	80/244 (33)
2	1/243 (<1)	0/244

Metastatic status n (%)		
Unresectable stage IIIC	21 (9)	13 (5)
M1a	40 (16)	40 (16)
M1b	40 (16)	42 (17)
M1c	146 (59)	152[c] (62)
Elevated lactate dehydrogenase n (%)	112/242 (46)	104/242 (43)
History of brain metastases n (%)	1 (<1)	2 (1)
BRAF-mutation genotype n (%)[d]		
V600E	170 (69)	174 (70)
V600K	24 (10)	32 (13)
Could not be evaluated	52[c] (21)	42 (17)

[a] Race was assessed by the investigator. [b] One patient randomly assigned to receive vemurafenib and cobimetinib had an ECOG performance-status score of 1 at randomisation but had an ECOG performance-status score of 2 after randomisation but before the first dose was received. [c] The CS reported fewer patients than the trial publication (n=153 and n=53 retrospectively). [d] After randomisation, tumour DNA was characterised to identify specific V600 mutations using next-generation sequencing. Cases that could not be evaluated were those in which either no tumour sample was provided or sequencing could not be performed on the tissue provided

Table 3 Ongoing trials

Trial identifier, sponsor	**Design, Country**	**Intervention, comparator, patient group**	**Expected end date**
NCT02427893; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins/ Genentech	Phase III, open label RCT (parallel assignment) USA	Vemurafenib monotherapy for 10 days, followed by combination therapy by adding cobimetinib vs cobimetinib monotherapy for 10 days, followed by combination therapy by adding vemurafenib – dosages not specified (total n=200). Adult patients with advanced unresectable American Joint Committee on Cancer stage III or stage IV BRAF V600E/K mutant melanoma.	August 2015 - final data collection date for primary outcome measure April 2017

3.1.4 Description and critique of the approach to validity assessment

The CS includes a quality assessment of the CoBRIM trial in Table 15 (CS pages 60 – 61) and second quality assessment of the trial in the 'Quality Assessment of trials included in NMA' in Table 76 (CS pages 204 – 208).

The company's quality assessment of the trial is appropriate, using NICE recommended criteria (based on the Centre for Reviews and Dissemination (CRD) guidance).[16] However, the two quality assessments of the CoBRIM trial differed in their conclusions. The first quality assessment of the trial states that "The study was of high quality based on the respective responses for each category thus indicating low risk of bias in study conduct and design" (CS page 60), while the second assessment in the CS states that the overall risk of bias for the trial is unclear (CS Table 76, page 208).

While there were some differences between the ERG's and the company's assessments of the trial quality (Table 4), the ERG agrees with the CS second quality assessment, in that the CoBRIM trial appears of unclear quality due to some lack of clarity in reporting and an imbalance in drop-outs between the treatment groups.

Table 4: Company and ERG assessment of coBRIM trial quality

CRD quality assessment criteria for RCT[16]	**Judgements[1]**		
	CS judgement (Table 15): **CS judgement (Table 76):**		**ERG judgement**
1. Was the method used to generate random allocations adequate?	CS Table 15: CS Table 76:	Not clear Not clear	Unclear
Comment: The trial journal publication only states that patients were randomly assigned in a 1:1 ratio and stratified according to geographic region and metastasis classification. As stated in the CS (CS Table 15, page 60), additional information in the trial protocol states that a stratified, permuted-block randomisation scheme would be used for treatment allocation based on stratification factors (Geographic region: North America, Europe, Australia/New Zealand/others; Metastatic classification: unresectable Stage IIIc, M1a, and M1b; or M1c). While block randomisation could be considered a low risk of introducing bias if carried out			

adequately, the details of the random sequence generation method are not provided; hence the risk of selection bias is unclear.			
2. Was the allocation adequately concealed?	CS Table 15: CS Table 76:	Yes Not clear	Unclear
Comment: The company's two quality assessments for this question differ. The ERG concluded that, as no details of treatment allocation sequence generation were reported (as stated in the company's second quality assessment), there is an unclear risk of selection bias. While the trial protocol mentions that an interactive response system would be used for random assignment, which suggests possible separation of the study investigators from those doing the randomisation, it is not completely clear if this was used.			
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	CS Table 15: CS Table 76:	Yes Yes	Yes
Comment: The CS stated that the characteristics of the patients at baseline were generally well balanced between the two study groups. While there were differences in patient's baseline characteristics between the treatment groups as previously stated (e.g. ECOG performance status, and metastatic status),[12] it was stated that there were no statistically significant differences between treatment groups (no p value reported) and expert clinical advice to the ERG suggests that these differences would not influence the improvements in clinical outcomes for those treated with cobimetinib.			
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	CS Table 15: CS Table 76:	Yes Not clear	Yes
Comment: The company's first quality assessment stated that there is a low risk of performance and detection bias in the trial as the investigator, patient, and sponsor were blinded to treatment assignment. However, this differs from their second assessment, which was that it is unclear. The trial was described as double-blinded, and the supporting text states that a blinded, independent central review of tumour assessments was performed. The ERG agrees with the company's first assessment, in that the trial appears to be at a low risk of performance and detection bias. The primary end-point was investigator-assessed PFS, but tumour assessments were reviewed by a blinded independent review committee (NB. there were some differences			

between the assessments, as reported in Section 3.3 of this report).			
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	CS Table 15: CS Table 76:	No Not clear	Yes
Comment: The company's two quality assessments for this question differ. Firstly, the company suggests that the imbalances in drop-outs between the groups were not unexpected, given that cobimetinib was anticipated to extend survival. In the second assessment, the company suggests that there was an unclear risk of attrition bias, stating that this is not reported. The ERG disagrees with both assessments due to differences in patient withdrawal between the two treatment groups (higher withdrawals in the vemurafenib + placebo group) and judges that there is a potential risk of attrition bias in the trial (see Table 15).			
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	CS Table 15: CS Table 76:	Not clear No	Unclear
Comment: The company's two quality assessments for this question differ. The first assessment suggests that the risk of reporting bias is unclear and this seems to be because only the primary, secondary and safety outcomes were reported in the primary trial publication.[10] The second assessment by the company suggests that there is no reporting bias, with all outcomes stated in the methods also reported in the results section. The ERG agrees with the company's first assessment, that the risk of reporting bias is unclear, as not all of the outcomes in the protocol have been reported; primarily there is little data in the CS for the EQ-5D-5L. (NB. These data were later supplied to the ERG on request, see Section 3.3.4 of this report).			
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS Table 15: CS Table 76:	Yes Yes	Yes
Comment: All the efficacy analyses were carried out in the ITT population, while the safety analyses were based on a modified ITT (mITT) population. A mITT population (all patients who underwent randomisation and received at least one dose of the study drug) omits those who may have had other relevant reasons for not receiving the drug. Modified ITT analyses for safety analysis are increasingly used in industry-sponsored trials[17].			

[1] The ERG used the CRD type responses (yes, no, unclear) to each question, although the CS approach differed slightly (yes, no, not clear).

3.1.5 Description and critique of the company's outcome selection

The outcomes specified in the CS are progression-free survival (PFS), overall survival (OS), response rates, adverse effects of treatment and HRQoL (CS Table 1, page 18). These are appropriate outcomes for evaluation of a cancer therapy, and are consistent with the final NICE scope.

The primary outcome is PFS, defined as the time from randomisation to either the first occurrence of disease progression, as assessed by the investigator according to Response evaluation criteria in solid tumours (RECIST) 1.1 criteria, or death from any cause (CS page 47).

Secondary outcomes are OS, response rates, PFS as assessed by independent review (two board certified radiologists), safety, and HRQoL (CS pages 47 - 50). Definitions provided in the CS are:

OS: The time from randomisation to death from any cause.

Overall response rate (ORR): For patients with measurable disease at baseline, investigator-assessed complete or partial response according to RECIST 1.1 criteria (CS page 48).

Best overall response rate (BORR): A complete response (CR) or partial response (PR) according to RECIST 1.1 criteria. Determined by two consecutive investigator assessments performed at least four weeks apart. For stable disease (SD), measurements had to meet SD criteria at least once post-randomisation at a minimum interval at least six weeks (CS page 48).

Duration of response (DOR): Evaluated in patients who satisfied BORR criteria. The time from a first occurrence of a documented CR until either disease progression as determined by investigator review (RECIST 1.1 criteria) or death from any cause (CS page 48).

Adverse events (AEs) were classified as: all AEs, drug related AEs, deaths, SAEs, drug-related SAEs, AESIs, and AEs leading to dose interruption/modification and to discontinuation of study treatment. The CS states that to classify AEs, the sponsor assigned preferred terms to the verbatim terms reported on the case report form, using the latest version of the Medical Dictionary for Regulatory Authorities (MedDRA 16.1) terminology. The CS does not state

whether AE classifications were checked or adjudicated independently. In addition to AEs, safety assessment included protocol-specified tests and vital signs. The AE classifications reported in the CS are generally consistent with those in the CSR, with some slight differences [redacted] (CS pages 48 – 49).

The instruments used to assess HRQoL were the European Organisation for Research and Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the EuroQol EQ-5D-5L questionnaires. These are both validated and widely-used HRQoL measures, and provide complementary information (QLQ-C30 is specific to cancer whilst EQ-5D is generic but provides utility estimates for use in the economic analysis) (CS page 49 - 50).

The ERG notes that although the QLQ-C30 is widely used in cancer research studies, it is not specific to skin cancer and might not necessarily be the most sensitive instrument for capturing effects of melanoma on patients' HRQoL. Several melanoma-specific instruments are available, including FACT-melanoma (Functional Assessment of Cancer Therapy-melanoma).[18]

In summary, the outcomes presented in the CS are appropriate for assessing effects of pharmacological therapy on melanoma and no important outcomes have been missed, although the cancer HRQoL instrument employed might not be the most sensitive of those available.

3.1.6 Description and critique of the company's approach to trial statistics

The rationale for the coBRIM trial sample size is provided on CS pages 50 - 51. The pre-specified number of progression events (206) required to give >95% power to detect a 5-month improvement in median PFS (from 6 months in the vemurafenib + placebo arm to 11 months in the vemurafenib + cobimetinib arm) was reached in May 2014 and the database was locked for PFS analysis on 10 July 2014. The final analysis of OS was to be performed after approximately 385 deaths had occurred, which would provide approximately 80% power to detect a 5-month improvement (from 15 months in the vemurafenib + placebo arm to 20 months in the vemurafenib + cobimetinib arm) in median OS (corresponding to a Hazard Ratio (HR) for death of 0.75).

The main analysis population for efficacy endpoints was the ITT population, defined as all randomised patients, regardless of whether or not study treatment was received (CS page 51).

Crossover between the treatment arms in the coBRIM trial was not permitted (CS Figure 3, page 43 and Table 12, page 57). The safety population was defined as all patients who received at least one dose of study treatment and analysed according to the treatment received (modified ITT, mITT). The population for analysis of HRQoL is referred to in the CS as the "PRO" population and was defined as all patients who had a baseline assessment and at least one post-baseline assessment. The CS (page 51) states that "the PRO population was analysed according to the treatment assigned at randomisation (i.e. ITT)". Dates for the first, second and final OS analysis are reported on page 52 and a summary of analysis dates for PFS, OS, response rates, and safety are reported in Table 8 (CS pages 42 - 43). There were no interim analyses for PFS.

The primary analysis compared PFS between the vemurafenib + cobimetinib and the vemurafenib + placebo arms of the coBRIM trial using a stratified log-rank test at overall significance 0.05 (2-sided). The HR for PFS was estimated using a Cox model stratified by geographic region (North America, Europe, Australia/New Zealand/others, where "others" appears to refer to Israel, whilst Russia and Turkey were included in the Europe subgroup according to the trial publication[12]) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; or M1c). Median PFS for each treatment arm was estimated based on Kaplan-Meier (KM) methods. Data from patients who experienced disease progression or death were censored at the last tumour assessment date. Data from patients with no post-baseline tumour assessment were censored at the randomisation date (CS page 53). The CS (page 54) states that three sensitivity analyses on the PFS outcome were performed (non-stratified analysis, censoring for non-protocol anticancer therapy, and censoring accounting for missed visits). Results of these sensitivity analyses are not reported in the CS, but were provided in response to a clarification request by the ERG.

OS was compared between the two treatment arms (CS page 54) using a log-rank test stratified by geographic region and metastatic classification, with significance level 0.05 (2 sided). The HR for death was estimated using a stratified Cox model. A Lan-DeMets implementation of an O'Brien-Fleming boundary function was used (although not stated in the CS, this controls for the Type I error associated with interim analysis of accumulating data). Data for patients still alive at the time of analysis were censored at the date the patient was last known to be alive. Survival time for patients with no post-baseline survival information was censored on the date of

randomisation. The duration of OS was calculated as the date of death or censoring minus the date of randomisation plus one day.

BORR was compared between the two treatment arms (CS page. 55) using a Chi-square test with Schouten correction. 95% CI were calculated for the BORR using the Clopper-Pearson method (a common method for calculating binomial confidence intervals) and for the BORR difference between treatment arms using the Hauck-Anderson method (one of a number of methods used to compute two-sided confidence intervals for difference between independent binomial proportions).

DOR was estimated (CS page 55) only for patients who had a confirmed overall response or partial response (i.e. CR or PR) and, being based on a subgroup, was not used for formal hypothesis testing. Medians and interquartile ranges for DOR were estimated using KM methods, with 95% CI calculated using the Brookmeyer and Crowley method.

HRQoL was assessed at baseline, days 1 and 15 in cycles 1 and 2, (C1D1; C1D15; C2D1; C2D15 respectively) and every other cycle thereafter until patient withdrawal or end of study using the EORTC QLQ-C30 (CS page 67). Data were evaluable until Cycle 8 Day 1 (C8D1), after which too few patients remained enrolled in the vemurafenib + placebo treatment arm to allow for meaningful conclusions (<25% from baseline).[19] HRQoL analyses (CS page 55) were post-hoc and based on descriptive statistics. In addition, responder analysis summarised the frequency of patients experiencing “clinically meaningful” improvement in each scale of the EORTC QLQ-C30 (symptoms, functional impact, and health-related quality of life). Clinically meaningful improvement was defined as a ≥10-point change at ≥1 post-baseline assessment.[19]

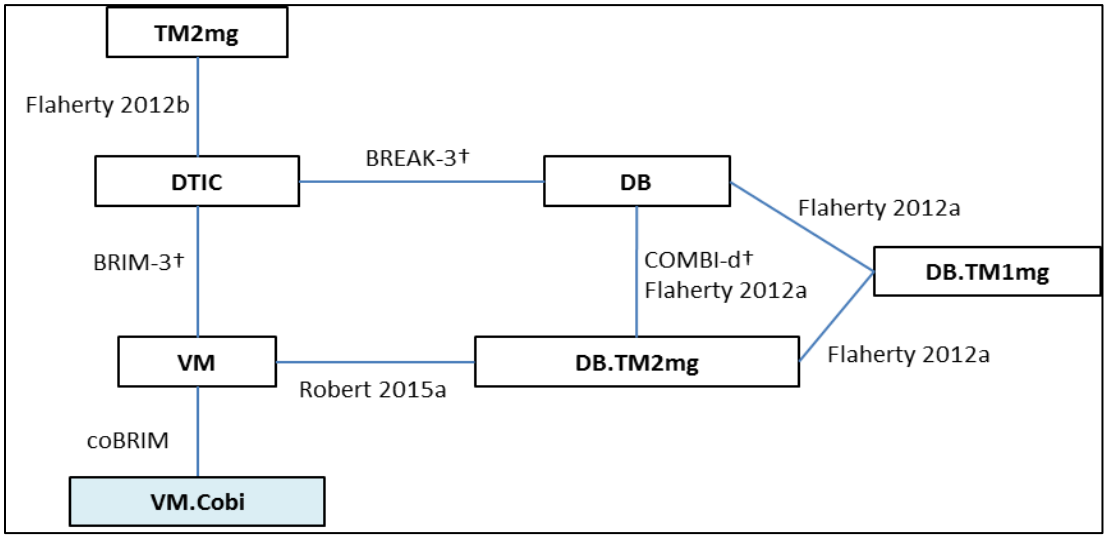
Exploratory pre-specified subgroup analyses for PFS and OS were conducted (see Section 2.3 of this report for details of the 12 subgroups).

In summary, the ERG considers that the approaches to statistical analysis and data censoring are appropriate. Some of the information in the CS is referenced as from the CSR, but has not been marked AIC or CIC and is not available in the coBRIM trial publication.[12]

3.1.7 Description and critique of the company's approach to the evidence synthesis

Given that only one trial of vemurafenib + cobimetinib (the coBRIM trial) was included in the CS, a meta-analysis was not possible. The submission therefore provides a narrative summary of that trial. The coBRIM trial did not include a dabrafenib monotherapy arm, and therefore to permit comparisons between vemurafenib + cobimetinib and dabrafenib an indirect comparison was necessary. A network meta-analysis (NMA) was conducted to make the indirect comparison and is described in CS section 4.10. The NMA provides pairwise indirect comparison results for the outcomes of OS and PFS (CS Tables 21 and Table 22, respectively), and these are used to inform the economic model (see Section 4.3.5 of this report).

An accelerated failure time model (AFT) was used (see below in Section 3.1.7.4 for a discussion of this) with the results presented as the inverse of the acceleration factor (1/AFT). For both outcomes, vemurafenib + cobimetinib was more effective than dabrafenib (see Section 3.3 of this report for a summary of the results of the NMA, and below for a critique of the use of the AFT). Figure 3 provides an illustration of the network, Table 5 details the interventions and comparators of the included trials, and Table 6 provides the ERG's critical appraisal of the NMA.



TM2mg = trametinib 2mg; DTIC = dacarbazine, DB = dabrafenib, VM = vemurafenib, DB.TM2mg = dabrafenib + trametinib 2mg; DB.TM1mg = dabrafenib + trametinib 1mg; VM.Cobi = vemurafenib + cobimetinib † Trial has more than one publication contributing data

Figure 3 Illustration of the network meta-analysis presented in the company submission (reproduced from CS Figure 11).

Table 5 Summary of the trials included in the company NMA (adapted from CS Table 20)

Trial reference	Trial arm A	Trial arm B	Trial arm C
coBRIM[12]	Vemurafenib + cobimetinib	Vemurafenib + placebo	
BRIM-3[20]	Vemurafenib	Dacarbazine	
Flaherty 2012a[21]	Trametinib 1mg + dabrafenib	Trametinib 2mg + dabrafenib	Dabrafenib
Flaherty 2012b[22]	Trametinib 2mg	Chemotherapy (dacarbazine or paclitaxel)	
BREAK-3[23]	Dabrafenib	Dacarbazine	
COMBI-d[24]	Trametinib 2mg + dabrafenib	Dabrafenib	
Robert 2015a (COMBI-v)[25]	Trametinib 2mg + dabrafenib	Vemurafenib	

Table 6 ERG appraisal of NMA

APPRAISAL CRITERIA	
Rationale and searches	
Is the rationale for the NMA and the study objectives clearly stated?	Yes, in CS section 4.10.2.
Does the reported study follow conventional guidelines for systematic reviews, as well as use explicit search terms, time frames, and avoid ad hoc data?	Yes, details given in Appendix 4 and Appendix 5. Searches were conducted of key databases; inclusion criteria are stated; PRISMA flow chart is provided; tabulated details of the included studies are given.
Are inclusion/exclusion criteria adequately reported?	Yes, CS appendix 4 (Table 70).
Is quality of the included studies assessed?	Yes, CS appendix 5 (Table 76).
Methods – Model	
Is the statistical model described?	Yes, Bayesian framework, but with limited information given.
Has the choice of outcome measure used in the analysis been justified?	Yes. PFS and OS are key outcomes in the scope and were primary outcomes for all the included studies.
Has the choice of fixed or random-effects model been justified?	Yes (CS section 4.10.17). The Deviance information criterion (DIC) was used to determine choice of model. The DIC indicated that fixed-effects models provided improved fit. However, further discussion of the assumptions about the distribution of study effects would have also been informative.

Has a structure of the network been provided?	Yes (CS Figure 11)
Is any of the programming code used in the statistical programme provided (for potential verification)?	Yes – WinBUGS code is provided in CS Appendix 8.
Methods - Sensitivity analysis	
Does the analysis conduct sensitivity analyses?	No.
Results	
Are the results of the NMA presented?	Yes.
Does the study describe an assessment of the model fit?	Yes - The model fit of the fixed- and random-effects models conducted for each outcome was compared using the deviance information criterion (DIC).
If direct and indirect evidence is reported to be consistent, is the evidence combined and the results presented?	Yes, the results of the NMA reflect both direct and indirect evidence. Z values are presented to confirm no evidence of inconsistency.
Has there been any discussion around the model uncertainty?	No
Are the point estimates of the relative treatment effects accompanied by some measure of variance such as confidence intervals?	Yes – 95% credible intervals are given around the NMA point estimates.
Discussion	
Does the study discuss both conceptual and statistical heterogeneity and incoherence?	No.
Does the discussion flow from the results seen?	No, little discussion is given.
Have the authors commented on how their results compare with other published studies (e.g. NMAs)?	No.

3.1.7.1 Evidence included in the NMA

The company did a systematic literature review to inform their indirect comparison. As stated in Section 3.1.1, the ERG considers that the search strategies are reasonable, but notes that the search is now nearly a year out of date. The ERG therefore updated the search and no additional relevant references were identified meeting the scope of the appraisal. The NMA can therefore be considered to be up-to-date and comprehensive in terms of the available published evidence.

The inclusion criteria for the NMA (CS Table 70) specified the interventions and comparators listed in the scope, plus additional comparators (e.g. targeted therapies such as pembrolizumab, trametinib; immunotherapy such as ipilimumab; and chemotherapy). The submission explains that the NMA was conducted to support pricing and reimbursement submissions across all markets, hence inclusion of these additional comparators in the systematic review conducted to support the NMA. The NMA as presented in the submission is for a 'restricted' scenario based

only on studies of patients who are BRAF mutation positive (n=7 RCTs, Figure 3 and Table 5). It is not explicitly stated in the CS but it is the ERG's assumption that the results of the restricted NMA scenario are not influenced by the additional comparators in the 'broad NMA'.

The restricted network, despite its narrowed focus on BRAF mutation positive patients, remains broader than the scope of the current appraisal as it contains trials of trametinib and dabrafenib combination therapy and trametinib monotherapy[21,22,24,25] (NB. these are the subject of a separate NICE technology appraisal in progress, ID661). The ERG assumes that these trials have been included for completeness and with the intention of adding to the volume of evidence in the network (particularly for the dabrafenib monotherapy node, where there is no direct comparison – see Figure 3 and Table 5 thus increasing precision of the results.

As Figure 3 shows, the network contains only one trial for each pairwise comparison (with the exception of trametinib and dabrafenib combination therapy versus dabrafenib, which is not a comparison within the scope of this appraisal). The network can therefore be considered to be sparse and its results should be considered with caution given the limited number of trials available.

The results are also dependent on the methodological quality and risk of bias of the included trials. The CS provides a quality assessment of the included trials in Appendix 5 (Table 76) using the CRD criteria. Each trial is summarised in terms of its overall risk of bias (though the Cochrane Risk of Bias criteria are not actually used). The overall judgement of bias was high in five of the seven RCTs. In the remaining two trials, the judgement was low and unclear respectively. The submission does not comment on the overall assessment of methodological quality and risk of bias of the included studies in relation to the results of the NMA, other than to state that removal of the high risk studies would have left only two remaining studies and therefore the indirect comparison would not have been possible. The ERG has not conducted an independent assessment of the risk of bias of the trials included in the NMA (other than the coBRIM trial, see section 3.1.4). The ERG notes that the company's overall risk of bias judgements do not appear to be consistent with the individual domains of bias identified for each study and also seem inconsistent between studies. Furthermore, the quality assessment judgements for the coBRIM trial in Table 15 and Table 76 of the CS disagree on four of the seven domains assessed (as discussed earlier, see Table 4). The ERG considers the company's assessment of the quality of the studies in the NMA to be unclear. However, it

should be noted that most of the trials in the network appeared to be relatively large phase III licensing RCTs, and some of these have been used to inform previous NICE appraisals of treatments for melanoma (BREAK-3 informed the company submission for NICE TA321 (dabrafenib),[7] and BRIM-3 informed the company submission for NICE TA269 (vemurafenib).[26]

3.1.7.2 Assessment of heterogeneity

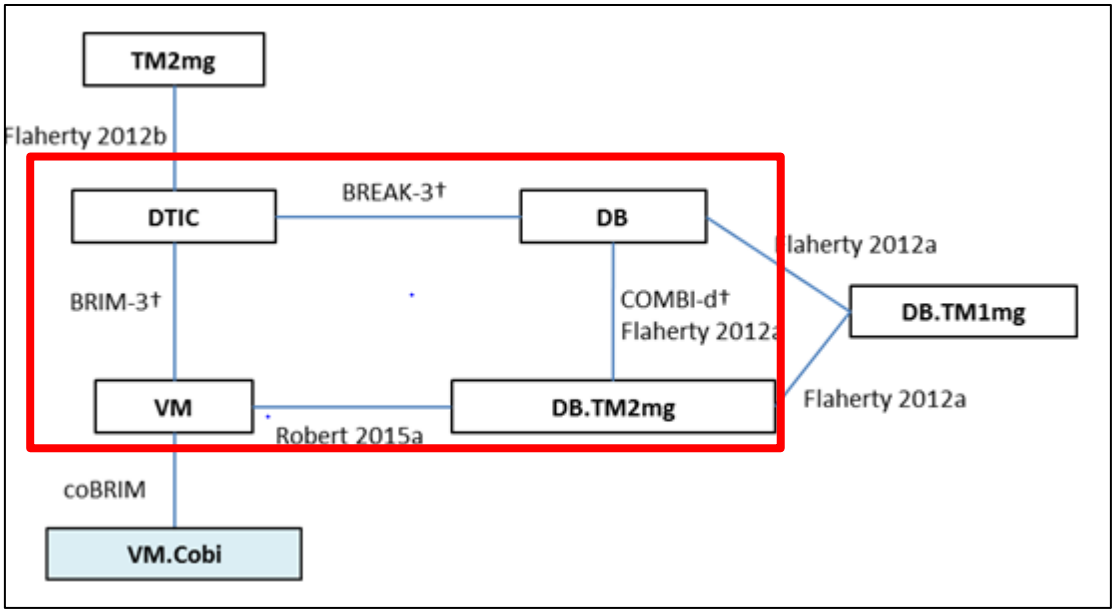
Heterogeneity is only briefly discussed in the CS. The submission states that each pairwise comparison was informed by a single trial, and therefore it was not possible to assess heterogeneity across studies per comparison (though as noted above, there was more than one study for the comparison with trametinib and dabrafenib combination therapy versus dabrafenib). The submission does not comment on conceptual heterogeneity amongst the trial network as a whole. In the ERG's assessment, the clinical trials in the network are broadly similar, as judged on the characteristics of the trials provided in CS Appendix 5 (Table 74). All trials included patients with unresectable stage III or IV melanoma with BRAF mutation, previously untreated with a BRAF or MEK (MAP extracellular signal-regulated kinases) inhibitor; generally had an ECOG status of 0 or 1 (approximately 60-70% of patients were classed as ECOG 0 across the trials); had adequate organ function (liver, kidney, cardiac); and the median age ranged from 49-58 years. These are selected trial characteristics from CS Table 74, however, there is no discussion in the CS about which of these factors (or others) may be regarded as treatment effect modifiers in patients with BRAF mutation positive advanced melanoma. Expert clinical advice to the ERG notes that LDH is an important prognostic and predictive factor, and that there was a higher proportion of patients with raised LDH (and therefore with an adverse prognosis) in the coBRIM trial than in the other major comparator studies (NB. The ERG has not checked the LDH values for the trials in the NMA as these data have not been provided in the CS).

The NMA was conducted according to the principle of a fixed effect. This assumes that the true treatment effect is common in all studies comparing the same treatments. In contrast, a random-effects model assumes that each study has its own true treatment effect, because study characteristics and the distribution of patient-related effect modifiers differ across studies. The submission reports that a fixed-effect model was chosen based on an assessment of model fit using the Deviance Information Criterion (DIC). The DIC is a standard method for assessing model fit in Bayesian models. The submission also justifies the use of fixed-effect because the network is small with a limited number of studies. A random-effects model, it is suggested in the

submission, would provide a poor estimate of the distribution of intervention effects (CS section 4.10.17). Other than this brief comment there is little further discussion about the assumptions to support the use of a fixed rather than a random-effects model. The issue of heterogeneity of effects across the studies is given little attention. Whilst use of the DIC to assess model fit is appropriate, the choice of model should also be guided by the plausibility of model assumptions. Methodological guidelines state that the assumptions of random-effects models are much more plausible than of fixed-effect models[27]. Notwithstanding the ERG's assessment above, that the studies in the network appear generally similar in selected patient and methodological characteristics, the submission provides little discussion of factors that might influence the distribution of effects between studies to support the justification of a fixed-effect model. Upon request from the ERG the company provided the random-effects NMA results for PFS and OS but only pairwise comparisons between dacarbazine and comparator drugs (clarification question A7). Whilst these results are not for all comparators in the NMA they illustrate that the point estimates for random-effects and fixed-effects were similar, though credible intervals (Crls) for the former were wider (as would be expected), and in some cases (e.g. dacarbazine versus vemurafenib + cobimetinib) included 1, indicating greater uncertainty. Taking this into account, along with the recommendations of methodological guidelines,[27] the ERG's view is that the random effects model should be the primary analysis. However, we have not been able to incorporate random effect estimates into our exploratory economic analyses (Section 4.4) as the company has only provided data for comparisons with dacarbazine.

3.1.7.3 Assessment of consistency

The submission states that there is one closed independent loop in the network (where comparisons are informed by both direct and indirect evidence) incorporating four treatments (dacarbazine; vemurafenib monotherapy; dabrafenib monotherapy; dabrafenib and trametinib 2mg). This is illustrated by the box on the left hand side in CS Figure 14, reproduced here in Figure 4).



TM2mg = trametinib 2mg; DTIC = dacarbazine, DB = dabrafenib, VM = vemurafenib, DB.TM2mg = dabrafenib + trametinib 2mg; DB.TM1mg = dabrafenib + trametinib 1mg; VM.Cobi = vemurafenib + cobimetinib

Figure 4 Illustration of the network meta-analysis presented in the company submission showing closed loop (CS Figure 14).

The Bucher method was used to assess consistency between direct and indirect evidence in the network.[28] This method estimates inconsistency as the difference between direct and indirect evidence in each closed loop of the network. The z-test[29] was used to assess the assumption of consistency. The submission states that there was no evidence of inconsistency based on z scores. The ERG considers that this method for assessing inconsistency is appropriate for a network of this type. Upon request from the ERG the company provided PFS and OS 1/AFT estimates for the indirect and the direct evidence comparisons (in the closed loop – the box in Figure 4) as derived from the Bucher method, to allow comparison of consistency (clarification response A8, Tables 16 and 17). The ERG notes that there is slight variation in the point estimates between the direct and the indirect evidence comparisons. Furthermore in some cases, notably for OS, the CrIs around the indirect point estimates included 1, in contrast to the direct evidence comparison where the corresponding intervals did not include 1. There were also occurrences of the opposite, thereby indicating no consistent pattern.

The clarification response reported absolute error values (differences between direct and indirect evidence on a log scale), and associated variance and p-values, which did not demonstrate evidence of inconsistency.

A key assumption in the NMA is that the dacarbazine or paclitaxel treatment node is considered to interact in the same way as dacarbazine in other trials (CS Page 79). (NB. refer to the top left hand corner of
Figure 3 for a graphic illustration of this node, marked 'DTIC', in relation to the rest of the network). This assumption is necessary to allow the trametinib monotherapy arm of the trial by Flaherty and colleagues 2012b[22] to connect to the network, via its chemotherapy comparator arm (patients in this arm could receive either dacarbazine or paclitaxel). The node combines the dacarbazine or paclitaxel arm from this trial with the dacarbazine arms of the BREAK-3 and BRIM-3 trials. The CS does not cite any evidence in support of this assumption.

In response to a clarification question from the ERG the company cited phase II trial results showing comparable efficacy of paclitaxel to dacarbazine in the treatment of melanoma (clarification question A6). At the request of the ERG the company provided a sensitivity analysis in which the trial by Flaherty and colleagues 2012b[22] was removed from the NMA. These results were very similar to the base case results of the NMA. The ERG is therefore satisfied that the assumption that the dacarbazine or paclitaxel treatment node is considered to interact in the same way as dacarbazine in other trials, and does not introduce bias into the network. Furthermore, expert advice to the ERG suggested that dacarbazine and paclitaxel can be regarded as clinically similar.

3.1.7.4 Analysis methods in the NMA

A Bayesian framework was used for the NMA, though there is little elaboration on how the model was constructed and analysed. For example, there is no mention of the choice of the prior probability distribution.

Though proportional hazards (PH) models are common in cancer, the CS reports results from an accelerated failure time model (AFT) for the NMA. The ERG therefore investigated which approach (AFT or PH) appears to be better justified given the properties of the underlying data

and the assumptions of each model, and whether the use of the AFT was likely to introduce any bias in favour or against any of the treatment alternatives under consideration.

Whilst PH models do not require specification of any form of the baseline hazard function, they do rely on the assumption of proportionality in hazards.[30] This assumption may not hold in some survival studies, and using PH models in situations where the PH assumption may not hold could result in serious bias.[30] Accordingly, the CS cites a recent NMA (sponsored by Roche and presented as a conference poster)[31], which found that the AFT model, which allows for nonproportional hazards over time, provides a better fit for metastatic melanoma drug trials as compared to the PH model (NB. vemurafenib + cobimetinib combination therapy was not included in this NMA as the coBRIM trial appears to pre-date the analysis). However, it needs to be noted that AFT models are predicated on the choice of a statistical distribution (here lognormal) and that covariates impact on survival by a constant factor. The literature states that parametric methods, such as AFT, may work better than PH models if the functional form of the distribution has been determined appropriately.[32]

In order to test the assumptions of the PH and AFT models, the CS reports log-cumulative hazards plots for PH and Q-Q plots for AFT (CS Appendix 6). The ERG agrees that cumulative hazards plots indicate a violation of the PH assumption, though it is not entirely clear whether Q-Q plots indicate a much better fit of the AFT model. Nevertheless, the ERG concluded that there is no reason to assume that the use of the AFT model is inappropriate in this particular context. Though PH models are more widely reported in the medical literature, AFT models appear to be adequate for the purpose of analysing survival data, and they may even perform better than PH models if the assumption of proportional hazards is violated.

The CS does not state whether the data included in the NMA were adjusted to take into account patient crossover between trial arms following disease progression. If crossover occurred this would lead to underestimation of any differences in effects between treatments, and thereby could disadvantage the experimental intervention. Methods have been developed which adjust for the effect of crossover, subject to plausible assumptions and the availability of mature outcome data.[33] These include the Rank Preserving Structural Failure Time method, the Inverse Probability of Censoring Weighting method, and the Iterative Parameter Estimation method. There is academic debate about which method is optimal for adjusting for crossover.[34] Crossover was not permitted in the coBRIM trial, but it was allowed in the BREAK-3[21] and

BRIM-3[18] trials which compared dabrafenib and vemurafenib (respectively) to dacarbazine. The proportions of patients who crossed over from dacarbazine to targeted BRAF inhibitor therapy were 57% and 34% in the BREAK-3 and BRIM-3 trials, respectively.[34] From the outcome data provided in CS Table 75 (Appendix 5) it appears that unadjusted estimates for PFS and OS were used in the NMA for these trials. Therefore, the respective effects of dabrafenib and vemurafenib compared against dacarbazine in the NMA are likely to have been underestimated. In the current appraisal this is of most significance for the comparison of dabrafenib against vemurafenib + cobimetinib where only indirect evidence is available. The ERG is unable to adjust the analyses to take into account patient crossover, but considers that unadjusted estimates which fail to account for crossover would disadvantage dabrafenib compared to vemurafenib + cobimetinib. The ERG explores this by providing a scenario analysis in which the clinical effectiveness of dabrafenib and vemurafenib is equal (Section 4.4.2).

3.1.7.5 Summary of the ERG appraisal of the NMA

The strengths of the NMA include:

- A comprehensive literature search to identify relevant evidence. The ERG is not aware of any additional studies that could be included.

The potential limitations of the NMA include:

- The network is sparse with each comparison of relevance to this appraisal informed by only one trial.
- The risk of bias was judged by the company to be high in several of the included trials, however, there is uncertainty about the reliability of the company's quality assessment judgements.
- There is little discussion of conceptual heterogeneity between the trials in the network, and whether there are differences between the trials in potential effect modifiers. The ERG's assessment of the data provided is that the trials are broadly comparable, based on selected characteristics presented.
- It appears that estimates for dabrafenib and vemurafenib from the BREAK-3 and BRIM-3 trials have not been adjusted to take into account the effect of patient crossover in those trials, likely underestimating the effect of these treatments compared to dacarbazine, with a consequent influence on their comparisons with vemurafenib + cobimetinib.

3.2 Summary statement of company's approach to evidence synthesis

Overall, the CS is reasonable in its quality of methodology and reporting, although the company does not appear to have applied quality assessment criteria consistently (Table 7).

Table 7 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes, consistent with the decision problem. For the NMA the population was restricted to patients treatment-naïve for metastatic disease. In response to a clarification request by the ERG (clarification question A9) the company stated that this restriction was to ensure study populations in the NMA were consistent with the coBRIM trial and the comparator studies.
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	Yes. The searches for studies in the NMA were approximately 1 year out of date. The ERG updated this search but did not identify any additional relevant evidence.
3. Is the validity of included studies adequately assessed?	Uncertain. Whilst the methods used to assess validity were appropriate, the conclusions about validity were different for the coBRIM trial depending on whether its validity was assessed in the CS as a single RCT or whether its validity was assessed as part of the NMA process. Most of the trials in the NMA were classed as being at high risk of bias, but the justification for this conclusion is unclear.
4. Is sufficient detail of the individual studies presented?	Yes for the pivotal coBRIM trial, but limited characteristics of patients in the trials included in the NMA were reported (only sex, age and performance status).
5. Are the primary studies summarised appropriately?	Yes, since only one RCT met the inclusion criteria a summary across primary studies is not applicable.

Eligibility criteria for the company's systematic review of clinical effectiveness are reported in CS Table 6 (page 38) and are appropriate for the decision problem. However, in their systematic review of studies for the network meta-analysis (NMA) the company limited inclusion criteria to patients who were treatment naïve when presenting with metastatic disease (CS Table 19, pages 74-75), without providing a justification.

The CS presents an extensive search for all relevant evidence using three major bibliographic databases (MEDLINE, Embase, and the Cochrane Library), and scrutiny of the proceedings of three international oncology conferences (CS page 37) (for complete details see Section 3.1.1 of this report). The systematic review of studies for the NMA was conducted in April 2015 and so nearly a year out of date. However, as stated earlier (Section 3.1.7) an update of this search by the ERG did not identify any additional relevant evidence. The clinical effectiveness review methods are clearly reported and appear adequate for minimising the risks of errors and bias in the evidence synthesis process (although the rationale for conclusions regarding risk of bias is unclear – see below). Study selection was conducted by two independent reviewers, whilst the data extraction and quality assessment steps were each conducted by one reviewer with checks made by a second reviewer.

The validity of the single included clinical effectiveness RCT (i.e. the coBRIM trial) was assessed using the CRD criteria (CS Table 15, pages 60 - 61). The validity of the eight trials included in the NMA was also assessed by the company using CRD criteria (CS Appendix 5, pages 204 - 208). Although the CRD questions are appropriate, the CS gives inconsistent answers for the coBRIM trial when it was assessed as the primary clinical effectiveness trial (Table 15 – overall low risk of bias) and when it was assessed as a contributor to the NMA (Appendix 5 – overall unclear risk of bias).

In Appendix 5 the company concludes that six of the eight trials included in the NMA were at high risk of bias but the CS does not provide a clear justification for this conclusion, and the CS does not mention study quality when considering the results of the NMA.

3.3 Summary of submitted evidence

3.3.1 Summary of results for progression-free survival

The CS (CS Table 16, page 63) presents results for three PFS analyses. These are the planned primary analysis of investigator-assessed progression with a data cutoff of 9 May 2014; a planned secondary analysis with the same cutoff date but with progression assessed by an independent review facility; and an unplanned post-hoc analysis of investigator-assessed progression based on a data cutoff of 16 January 2015. The planned analyses are specified in the published study protocol,[12] whilst the post-hoc analysis is reported in a conference presentation[15] (Table 8). According to the CS (page 52), no interim analyses of PFS were planned or performed. Median follow-up in the vemurafenib + cobimetinib group was 7.3 months in the pre-planned analysis and 14.9 months in the post-hoc analysis.

The planned and post-hoc analyses of PFS all favour vemurafenib + cobimetinib over vemurafenib + placebo, with HRs that are statistically significant (p<0.001 and/or the HR 95% confidence interval excludes 1). The median survival difference between the cobimetinib and placebo arms ranged from 3.7 months (HR=0.51; primary analysis, investigator-assessed progression) to 5.3 months (HR=0.60; secondary analysis, independent review board assessed progression). The primary analysis gives a more conservative estimate of PFS than the independent review board assessment, though both were reported to have been blinded to treatment allocation. The former analysis is preferred by the ERG as it was designated as the primary analysis. Results of the post-hoc update analysis are similar to those of the planned secondary analysis (Table 8), although did not include a p value.

Table 8 PFS: primary, secondary and updated analyses

Analysis	Vemurafenib + cobimetinib (n=247)	Vemurafenib + placebo (n=248)
Primary: PFS assessment by investigator - Data cutoff 9 May 2014[12]		
PFS events, n (%)	Not reported	Not reported
Median follow-up, months	7.3	7.3
Median duration, months (95% CI)	9.9 (9.0 – NR)	6.2 (5.6 – 7.4)
HR for death or disease progression	0.51 (0.39 – 0.68);[a]	Reference

(95% CI)	p<0.001	
Secondary: PFS assessment by independent review facility - Data cutoff 9 May 2014[12]		
PFS events, n (%)	Not reported	Not reported
Median follow-up, months	Not reported	Not reported
Median duration, months (95% CI)	11.3 (8.5 to NR)	6.0 (5.6 – 7.5)
HR for death or disease progression (95% CI)	0.60 (0.45 – 0.79);[a] p<0.001	Reference
Post-hoc update: PFS assessment by investigator - Data cutoff 16 January 2015[15]		
PFS events, n (%)	143 (57.9)	180 (72.6)
Median follow-up, months	14.9	13.6
Median duration, months (95% CI)	12.3 (9.5 – 13.4)	7.2 (5.6 – 7.5)
HR for death or disease progression (95% CI)	0.58 (0.46 – 0.72)[a]	Reference

NR, Not reached
[a] Analysis was stratified according to geographic region and metastasis classification.

3.3.1.1 Sensitivity analyses on PFS

The following sensitivity analysis results (Table 9) are not reported in the CS; they were provided by the company in response to a clarification request from the ERG. These analyses were conducted based on the primary PFS analysis of investigator-assessed progression with a cutoff date of 9 May 2014. The CS states that the company planned three sensitivity analyses: a non-stratified analysis; an analysis in which patients who received non-protocol therapy were censored; and an analysis in which patients with missed visits were censored. The company's response to the clarification request shows that the second analysis (censoring for non-protocol anti-cancer therapy) was in fact split into stratified and non-stratified analyses (Table 9). The company's response also states that the proposed third sensitivity analysis (censoring accounting for missed visits) was not conducted due to low patient numbers.

Table 9 Results of sensitivity analyses on PFS

Median PFS (95% CI)	Cobimetinib + vemurafenib (n=247)	Vemurafenib + placebo (n=248)	HR for progression (95% CI)
Reference analysis (from	9.9 (9.0 – NE)	6.2 (5.6 – 7.4)	0.51 (0.39 – 0.68);

Table 8 above)			p<0.001
Non-stratified analysis	9.9 (9.0 – NE)	6.2 (5.6 – 7.4)	0.51 (0.39 – 0.68[b]); p<0.001
PFS censored for non-protocol anti-cancer therapy: stratified analysis[a]	11.1 (9.0 – NE)	6.2 (5.6 – 7.4)	(0.51 (0.38 – 0.67); p<0.0001
PFS censored for non-protocol anti-cancer therapy: non-stratified analysis	11.1 (9.0 – NE)	6.2 (5.6 – 7.5)	(0.51 (0.38 – 0.68); p<0.0001

NE, Not evaluable

[a] stratification by geographical region and metastasis classification

[b] Company clarification text states upper limit of 95% CI is 0.89 but company clarification table states upper limit is 0.68

As shown in Table 9, the non-stratified analysis had no impact on the results. The analyses censoring for non-protocol anti-cancer therapy increased median PFS in the vemurafenib + cobimetinib group only, but this has no discernible impact on the hazard ratio. The ERG would expect that varying these analyses would have influenced the hazard ratios and their 95% CIs, but the company provided no explanation for the results being nearly identical.

3.3.1.2 NMA results for PFS

As discussed earlier (Section 3.1.7.4) the NMA estimated the effect of the comparisons using an AFT model. Results are expressed as the inverse of the acceleration factor (1/AFT). Accordingly:

- 1/AFT of 1 indicates there is no difference between the treatment and control
- 1/AFT < 1 favours treatment
- 1/AFT >1 favours control

CS Table 22 provides results for PFS for all comparators in the NMA. The fixed-effect 1/AFT for vemurafenib + cobimetinib compared to dabrafenib was 0.60 (95% CrI 0.46 to 0.77) and compared to vemurafenib it was 0.63 (95% CrI 0.53 to 0.76), indicating that combination therapy is more beneficial in terms of PFS than both comparators.

3.3.2 Summary of results for overall survival

The CS (pages 64 - 65) presents results for three OS analyses. These are the first interim analysis with a data cutoff of 9 May 2014; the second interim analysis with a data cutoff of 16 January 2015; and the planned final analysis which had a data cutoff of 28 August 2015 (Table 10). Although the CS specifies OS as being a secondary endpoint (CS page 64), criteria are given for ensuring an adequate sample size for 80% statistical power: the final analysis of OS was to be performed after approximately 385 deaths had occurred (see ERG section 3.1.6). The ERG notes that the total number of events which had occurred in both combined study groups at the final analysis data cutoff was 255 (Table 10), meaning that this outcome analysis would likely have been underpowered.

Table 10 OS: interim and final analyses

Analysis	Vemurafenib + cobimetinib (n = 247)	Vemurafenib + placebo (n = 247)
Interim analysis: Data cutoff 9 May 2014[12]		
OS at 9 months, % (95% CI)	81 (75 - 87)	73 (65 - 80)
Median OS duration, months (95% CI)	NR	NR
HR for death (95% CI)	0.65 (0.42 – 1.00)[a]	Reference
p-value	0.046	Reference
Interim analysis: Data cutoff 16 January 2015 (CS Table 17 and draft SmPC)		
OS at 12 months, % (95% CI)	74.9 (69.3 – 80.5)	63.0 (56.8 – 69.3)
Median OS duration, months (95% CI)	NE (20.7 – NE)	17.0 (15.0 – NE)
HR for death (95% CI)	0.65 (0.49 – 0.87)[a]	Reference
p-value	Not reported	Not reported
Final analysis: Data cutoff 28 August 2015[13]		
OS events, n (%)	114 (46.2)	141 (56.9)
Median OS duration, months (95% CI)	22.3 (20.3 - NE)	17.4 (15.0 - 19.8)
Hazard ratio for death (95% CI)	0.70 (0.55 - 0.90)[a]	Reference
p-value	0.005	Reference

NE = not evaluable; NR = not reached.
[a] Patients were stratified according to geographic region and metastasis classification
NB HR for updated analysis (16 January 2015) 0.65 (95% CI 0.49 – 0.87); reported in CS but source unclear

All three OS analyses appear to favour vemurafenib + cobimetinib over vemurafenib + placebo (Table 10). In the published interim analysis,[12] the proportion surviving to 9 months was marginally higher (8%) in the vemurafenib + cobimetinib group, and although the HR appears favourable (0.65) it has high uncertainty, with an upper CI of 1. In the final analysis, despite the planned number of events not being reached, meaning that the analysis was likely underpowered, patients in the vemurafenib + cobimetinib group had a median survival 4.9 months longer than in the vemurafenib + placebo group with the HR (0.70) being statistically significant (p = 0.005).

3.3.2.1 Sensitivity analyses on OS

The CS does not mention sensitivity analyses for OS. However, a sensitivity analysis on OS was provided in the company's response to the ERG's clarification request about PFS analyses (clarification request question A2). This compared stratified and non-stratified analyses for investigator-assessed OS with a data cutoff of 28th August 2015 (i.e. the planned final analysis data set). This analysis had no impact on the results other than to slightly alter the 95% CI of the HR (stratified: 0.55 – 0.90; unstratified: 0.54 – 0.89). The company's clarification also stated that a planned sensitivity analysis of OS censored for subsequent anti-cancer therapy was not conducted because there were no patients in the vemurafenib + placebo group who had crossed over to cobimetinib at the time of the final OS analysis. The reason for this statement seems unclear, given that a similar analysis was reported by the company for PFS and also that crossovers were not permitted, and therefore would not have been expected, in the coBRIM trial.

3.3.2.2 NMA results for OS

CS Table 21 provides results for OS for all comparators in the NMA. The fixed-effect 1/AFT for vemurafenib + cobimetinib compared to dabrafenib was 0.63 (95% CrI 0.47 to 0.86), and compared to vemurafenib it was 0.73 (95% CrI 0.59 to 0.90), indicating that combination therapy is more beneficial in terms of OS than both comparators.

3.3.3 Summary of results for response rates

The CS (pages 65 - 67) presents results for two analyses of response rates. These are for the published planned analysis which had a data cutoff of 9 May 2014 and a post-hoc updated analysis with a data cutoff of 16 January 2015 (Table 11). The proportion of patients who experienced an objective (i.e. complete or partial) response was significantly higher in the vemurafenib + cobimetinib group (68%) compared to the vemurafenib + placebo group (45%), although the ERG notes that the majority of these patients had a partial rather than complete response.

Table 11 Response rates outcomes: primary and updated analyses

Analysis	**Vemurafenib + cobimetinib (n = 247)**	**Vemurafenib + placebo (n = 248)**
Planned analysis: Data cutoff 9 May 2014[12]		
Complete response, n (%) Partial response, n (%) Stable disease, n (%) Progressive disease, n (%) No complete response or progressive disease, n (%) Could not be evaluated, n (%)	25 (10) 142 (57) 49 (20) 19 (8) 0 12 (5)	11 (4) 100 (40) 105 (42) 25 (10) 1 (<1) 6 (2)
Complete or partial response Percent of patients (95% CI) p-value	(n = 167) 68 (61 – 73) <0.001	(n = 111) 45 (38 – 51) Reference
Median duration of response, months (95% CI)	NR (9.3 – NR)	7.3 (5.8 – NR)
Post-hoc updated analysis: Data cutoff 16 Jan 2015[15]		
Complete response, n (%) Partial response, n (%)	39 (16) 133 (54)	26 (11) 98 (40)
ORR (complete or partial response) Percent of patients (95% CI) Difference in ORR, % (95% CI)	(n = 172) 69.6 (63.49 - 75.31) 19.64 (10.95-28.32)	(n = 124) 50.0 (43.61 - 56.39) Reference

Duration of response (DOR)		
Patients with event, n (%)	84 (48.8)	73 (58.9)
Median DOR, months (95% CI)	12.98 (11.10 - 16.62)	9.23 (7.52 - 12.78)
Range	2.86 - 20.11	1.77 - 17.68

NR, Not reached.
[a] Response could not be evaluated for patients who withdrew consent, were withdrawn by site investigator, died or started new anticancer therapy before the first tumour assessment.

3.3.4 Summary of results for health related quality of life

The CS presents a brief, narrative description of patients' HRQoL (CS pages 67 - 69), based on the EORTC QLQ-C30 as applied within the coBRIM trial, and reported in a poster by Dréno and colleagues.[19] The only quantitative HRQoL results reported in the poster are line charts showing percentage changes from baseline in different subscales of the QLQ-C30, and a histogram showing the percentage of patients with clinically meaningful improvement in scores for each QLQ-C30 subscale.[19] Only the histogram is included in the CS and this is reproduced in Figure 5 below. The CS points out that the analysis was considered exploratory, with patients deemed to have experienced a clinically meaningful improvement in HRQoL if the QLQ-C30 score improved by at least 10 points (a ≥10-point increase in scores for global health status and functioning scales, or a ≥10-point decrease in scores for symptom scales) at one or more post-baseline assessments. The CS does not clarify whether this 10-point threshold is arbitrary or based on validation studies.

The CS points out that the QLQ-C30 scores do not capture patients' HRQoL post disease progression since few patients completed the QLQ-C30 questionnaire upon discontinuation of study treatment (CS page 69). However, it is not reported how many patients did complete the questionnaire upon discontinuation and whether their responses were analysed.

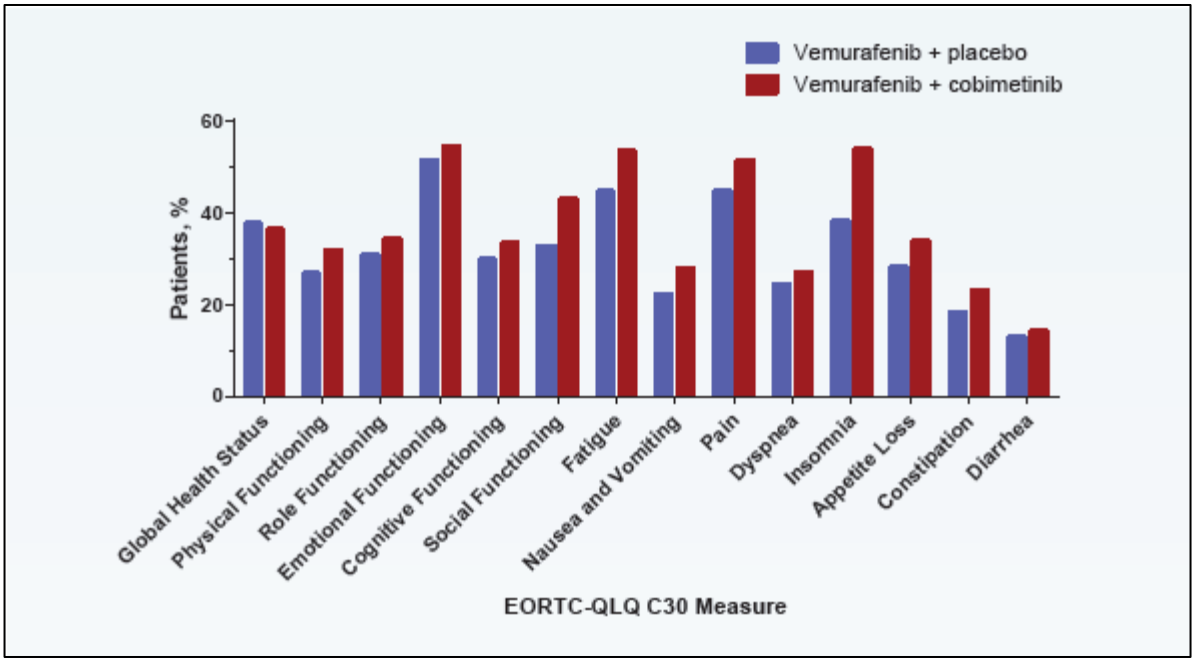


Figure 5 Clinically meaningful improvement in HRQoL (QLQ-C30 score change ≥10 points relative to baseline)

As shown in Figure 5, for many scales of the QLQ-C30 the frequency of patients with clinically meaningful improvement in the QLQ-C30 subscales was higher in the vemurafenib + cobimetinib group, with the largest difference being for the insomnia subscale. However, it is unclear whether these differences between study groups would be statistically significant and the analysis provides no indication of the durability of these improvements across the course of patients' therapy.

The CS concludes that patients experienced clinically meaningful improvement in insomnia relative to baseline only in the vemurafenib + cobimetinib group. The CS also concludes that patients in the vemurafenib + cobimetinib group experienced clinically meaningful worsening of diarrhoea from baseline to C2D15 but not in subsequent cycles, without any concomitant change in diarrhoea scores in the vemurafenib + placebo group. These conclusions are consistent with line charts presented in the poster by Dréno and colleagues[19] (not reproduced here). However, the ERG cautions that these results are uncertain since all comparisons reported in the line charts[19] have very wide (unspecified) error bars. Also, the number of patients providing QLQ-C30 scores at each sampling point is not reported.

In response to a request by the ERG (clarification question B2), the company provided details of the EQ-5D values obtained from the coBRIM trial. Utilities were collected in coBRIM using the EQ-5D-5L and were mapped to their equivalent EQ-5D-3L values using a crosswalk method. The ERG considers this approach to be appropriate, as the EQ-5D-3L is widely used and is the standard utility estimation method in other related NICE technology appraisals. The EQ-5D was completed mostly by patients who had not progressed (see Section 4.3.6.1 of this report).

In their clarification response, the company provided the estimates of mean and median EQ-5D-3L scores and the 95% CI of the mean for day 1 of the first and second cycles and then for day 1 of every other cycle up to cycle 22, as well as for the end of study treatment (clarification response Table 19). The mean utility estimates were summarised graphically (Figure 6 in the clarification response) and are reproduced below in [redacted].

[redacted]

The ERG notes that the HRQoL analysis in coBRIM would be statistically under-powered for detecting differences between the treatment arms and according to the company's response (clarification Table 19), the 95% CI of the mean utility estimates for both arms (not shown in [redacted]) would overlap for all sampling times. However, there appears to be a trend for improved HRQoL in the vemurafenib + cobimetinib arm from cycle 2 to cycle 18. These results

are increasingly uncertain after cycle 18 due to the low number of utility estimates available (for vemurafenib + cobimetinib these are n=27 at C18D1; n=9 at C20D1, and n=2 at C22D1).

Overall, taking together the QLQ-C30 and EQ-5D results there appears to be some pre-progression HRQoL benefit associated with vemurafenib + cobimetinib compared to vemurafenib + placebo, but this is based on an analysis that was unable to demonstrate statistical significance. It is unclear whether the slightly higher utility estimates in the vemurafenib + cobimetinib arm reflect HRQoL improvements resulting from less insomnia and/or other factors (e.g. the incidence of non-melanoma skin cancers which was lower in the vemurafenib + cobimetinib arm). The trend for slightly higher pre-progression utilities in the vemurafenib + cobimetinib arm, and the uncertainty associated with these, is captured in the economic model through these utility estimates and their 95% CIs (see Section 4 of this report).

3.3.5 Summary of results for sub-group analyses

The CS reports results of 12 subgroup analyses (as listed above, section 2.3). These are presented as forest plots showing nine subgroup analyses for PFS (CS Figure 9, page 71) and three subgroup analyses for OS (CS Figure 10, page 71) (the CS does not justify why the same subgroups were not analysed for each outcome). Hazard ratios are consistently below 1.0 for all the subgroup analyses reported, although for some subgroups with small sample sizes the 95% CI includes 1.

Overall, all the subgroups analysed gave broadly similar responses to the vemurafenib + cobimetinib therapy when compared against vemurafenib + placebo. However, given that the 12 subgroup analyses were split (9 analysed for PFS, 3 analysed for OS) rather than all subgroups being analysed for both outcomes, there is some uncertainty as to whether these results are fully representative and generalisable across both outcomes.

3.3.6 Summary of adverse events

The safety population was analysed according to the study treatment received; however, eight patients assigned to the vemurafenib + placebo group received investigational cobimetinib instead of placebo as a result of dispensing errors. Two patients (one in each study group) were excluded from the safety analysis as they did not receive the assigned study drug.

The CS reports AEs according to their frequency (CS Table 23, page 86), consistent with the trial journal publication,[12] and also lists those AEs that led to discontinuation or dose modification (CS Table 24, pages 87 - 88), partly consistent with a poster by Dréno and colleagues.[14] In response to a clarification request by the ERG the company provided: a table showing the most frequent serious AEs; a table showing grade ≥3 AEs that had the largest differences (≥2%) between the study arms; and a table showing the primary reasons why patients discontinued from the coBRIM trial. Due to the different ways these AEs are grouped in each table it is not always easy to see clear patterns. We have reproduced these tables below, considering first the frequency of occurrence of AEs and then the factors that led to patient discontinuation.

3.3.6.1 Frequency of adverse events and differences between trial arms

The most frequent AEs are shown separately by grade (1 - 4) in Table 12 (taken from CS Table 23, page 86 and consistent with the trial journal publication[12]). No individual grade 4 AEs exceeded 1% frequency, except for grade 4 elevation of creatine kinase which occurred in 4% of patients in the vemurafenib + cobimetinib arm. The most frequent grade 3 AEs were the elevated enzymes: alanine aminotransferase (11% and 6% of patients in the cobimetinib and placebo arms respectively); aspartate aminotransferase (8% and 2% respectively); and creatine kinase (7% and 0% respectively). The most frequent AEs occurring at grades 1 - 2 were diarrhoea, nausea and rash.

In Table 12 the row for patients experiencing “Any adverse event” has a specific interpretation in the trial publication and CS and should be not interpreted to literally mean “any” AE (see Table 12 footnote). If a patient had multiple AEs these are counted in the “Any adverse events” row only once, in the column for which the highest grade of event occurred. For example, in the vemurafenib + cobimetinib arm, the “Any adverse event” row shows that 19 patients (7%) had AEs no greater than grade 1; 66 patients (26%) had AEs up to and including grade 2; 125

patients (49%) had AEs up to and including grade 3; whilst 34 patients (13%) had AEs up to and including grade 4 (Table 12). Only grade 2 AEs were higher in the vemurafenib + placebo group (29%) than those in the vemurafenib + cobimetinib group.

Table 12 Most frequent adverse events (occurring in ≥20% of patients in either group)

Adverse event, n (%)	Vemurafenib + cobimetinib (n = 254)				Vemurafenib + placebo (n = 239)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Any adverse event	19 (7)	66 (26)	125 (49)	34 (13)	21 (9)	70 (29)	117 (49)	22 (9)
Diarrhoea	99 (39)	29 (11)	16 (6)	0	51 (21)	16 (7)	0	0
Nausea	75 (30)	22 (9)	2 (1)	0	43 (18)	12 (5)	2 (1)	0
Vomiting	41 (16)	10 (4)	3 (1)	0	21 (9)	6 (3)	2 (1)	0
Rash	55 (22)	29 (11)	13 (5)	2 (1)	46 (19)	27 (11)	12 (5)	0
Photosensitivity reactions	48 (19)	18 (7)	6 (2)	0	25 (10)	12 (5)	0	0
Hyperkeratosis	23 (9)	3 (1)	0	0	49 (21)	14 (6)	5 (2)	0
Fatigue	48 (19)	24 (9)	9 (4)	0	42 (18)	24 (10)	7 (3)	0
Pyrexia	49 (19)	13 (5)	4 (2)	0	43 (18)	10 (4)	0	0
Arthralgia	54 (21)	23 (9)	6 (2)	0	53 (22)	31 (13)	12 (5)	0
Alopecia	33 (13)	1 (<1)	1 (<1)	0	55 (23)	14 (6)	1 (<1)	0
Increased alanine amino-transferase	16 (6)	15 (6)	28 (11)	1 (<1)	17 (7)	11 (5)	14 (6)	1 (<1)
Increased aspartate amino-transferase	17 (7)	18 (7)	21 (8)	0	15 (6)	10 (4)	4 (2)	1 (<1)
Increased creatine kinase	23 (9)	27 (11)	17 (7)	9 (4)	6 (3)	1 (<1)	0	0

Multiple occurrences of a specific adverse event for a patient were counted once at the highest grade of the occurrence (based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0), e.g. if a patient had two episodes of a specific toxic event, one grade 3 and one grade 4, the patient was counted only once in the grade 4 column. This applied also to "Any adverse events", e.g if a patient had three separate events of grade 1, 3, and 4, the patient was counted only once in the grade 4 column.

The CS states (page 87) that the majority of first grade ≥3 AEs occurred early in treatment, with a median time to onset among patients with grade ≥3 AEs of 0.53 months for vemurafenib + cobimetinib and 0.79 months for vemurafenib + placebo. After the first cycle (28 days), the incidence of grade ≥3 AEs decreased over time. The median time to resolution for grade ≥3 AEs that occurred in the first 28 days was 0.5 months for both arms.

Overall, six deaths were attributed to AEs in the vemurafenib + cobimetinib arm and three deaths in the vemurafenib + placebo arm (CS page 89). In the vemurafenib + cobimetinib arm,

the AE was recorded as the primary cause of death for two patients (cardiac arrest and pneumonia). An additional two patients had primary cause of death recorded as “other” (unexplained; asthenia and fatigue). The remaining two patients had disease progression recorded as the primary cause of death.

Of the three deaths in the vemurafenib + placebo arm, cardiac failure was the reported cause for one patient and disease progression was documented as the cause of death for the other two patients.

Two patients, one in each treatment arm, died as a result of AEs that were considered by the investigator to be related to study treatment: One patient in the vemurafenib + cobimetinib arm (fatigue and asthenia) and one patient in the vemurafenib + placebo arm (cardiac failure).

The most frequent serious adverse events (SAEs) are shown in Table 13 (taken from the company’s clarification response).

[redacted]*

Table 13 [redacted]

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

A clearer indication of how AEs differed between the cobimetinib and placebo arms of the coBRIM trial is shown in Table 14 (taken from the company's clarification response).

Table 14

Cob: cobimetinib; NR, not reported; Vem: vemurafenib; ↑ elevated
NB. This table has been redrawn from Table 2 and Table 3 in the company's clarification response to show AEs ordered according to their difference between the trial arms.

Although retinal detachment was relatively uncommon, it appears to have only affected patients in the cobimetinib arm (Table 13 and Table 14). However, the company in their clarification response did not provide the frequency of retinal detachment for the latest data cutoff (Table 14).

3.3.6.2 Reasons for treatment discontinuation

The primary reasons for treatment discontinuation, i.e. factors including but not limited to AEs, are not presented in the CS but were provided in the company's clarification response (Question A1) and are reproduced below in Table 15.

Table 15

[redacted]

[redacted]

The AEs which led to patient discontinuation are reported in the CS (CS Table 24, pages 87 - 88), and in a poster reported by Dréno and colleagues,[14] and are reproduced below in Table 16.

Table 16 Adverse events leading to discontinuation or dose modification

AE, n (%) (n=493)	Incidence (all grades)		Discontinuation		Reduction[a]		Interruption	
	Vem + Cob	Vem + placebo	Vem + Cob	Vem + placebo	Vem + Cob	Vem + placebo	Vem + Cob	Vem + placebo
Diarrhoea	144 (57)	67 (28)	0	1 (<1)	6 (2)	0	14 (6)	6 (3)
Photosensitivity	105 (41)	75 (31)	0	0	0	0	3 (1)	1 (<1)
Rash	182 (72)	157 (66)	8 (3)	2 (1)	10 (4)	9 (4)	13 (5)	17 (7)
Elevated CPK	76 (30)	8 (3)	1 (<1)	0	0	2 (1)	4 (2)	0
Liver laboratory value abnormalities	101 (40)	76 (32)	8 (3)	3 (1)	4 (2)	3 (1)	9 (4)	5 (2)
Serous retinopathy	61 (24)	5 (2)	3 (1)	0	2 (1)	0	9 (4)	0
Cutaneous	10 (4)	42 (18)	0	0	0	0	0	3 (1)

neoplasm[b]								

Cob: cobimetinib; Vem: vemurafenib
[a] Interruption or reduction of both drugs for AEs occurred in 42% of patients in the vemurafenib + cobimetinib arm and in 33% of patients in the vemurafenib + placebo arm
[b] Implied in the CS (page 87) that this refers to secondary cutaneous squamous cell carcinoma and keratoacanthoma

The CS lists 7 AEs as leading to discontinuation: diarrhoea, photosensitivity, rash, elevated creatine phosphokinase (CPK), liver laboratory abnormalities, serous retinopathy, and cutaneous neoplasm, as shown in Table 15. These categories are slightly different to those reported elsewhere in the CS and the company's clarification response. It is unclear whether the category "serous retinopathy" includes both retinal detachment and chorioretinopathy.

There appear to be discrepancies between the discontinuations due to AEs reported in the company's clarification response (ERG Table 15), those reported in the CS (ERG Table 16) and a poster presentation reported by Dréno and colleagues.[14]

[redacted] However, in the CS (as reproduced in ERG Table 16) the total number of discontinuations in the vemurafenib + cobimetinib arm is only 20. The poster presentation[14] states that in the vemurafenib + cobimetinib arm 45 patients had an AE leading to drug withdrawal, of which 32 (71%) withdrew both drugs, whereas 10 (22%) and 3 (7%) withdrew cobimetinib or vemurafenib alone, respectively. Similarly, the numbers of patients withdrawing vemurafenib and/or placebo in the comparator arm differs between Table 15 and Table 16 and the poster, which reports 35 patients who had an AE leading to drug withdrawal, of whom 30 (86%) withdrew both drugs, whereas 3 (9%) and 2 (6%) withdrew placebo or vemurafenib alone, respectively.[14] It is unclear whether these differences are related to different analysis times.

According to the poster presentation by Dréno and colleagues,[14] in both arms, most patients who discontinued study treatment for AEs withdrew from both study treatments at the same time. The poster also states that of 10 patients in the vemurafenib + cobimetinib arm who withdrew cobimetinib alone, 6 cases of withdrawal were at least partly a result of serous retinopathy (SR). The poster also states that no AE of any single preferred term led to discontinuation of either drug in >4.0% of patients.

3.4 Overall summary of clinical effectiveness

The ERG considers that the CS presents a generally unbiased estimate of the treatment effect of vemurafenib + cobimetinib combination therapy for patients with advanced melanoma within the stated scope of the decision problem. The company's systematic review of clinical effectiveness followed standard procedures and is of good quality. The ERG is not aware of any additional relevant published trials that could be included. The key RCT, coBRIM, is generally well-designed and provides an appropriate evidence base to inform the assessment of clinical and cost-effectiveness in this appraisal. The trial showed statistically significant differences in favour of vemurafenib + cobimetinib compared to vemurafenib monotherapy in terms of measures of survival and treatment response, with a generally favourable safety profile. The NMA enabled indirect comparisons to be made between vemurafenib + cobimetinib and dabrafenib. This showed that vemurafenib + cobimetinib was more favourable on measures of survival. However, the evidence network was sparse, with only one trial informing each comparison, and there was no discussion of clinical heterogeneity between the trials in the network.

4 COST EFFECTIVENESS

4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

i) a review of published economic evaluations of vemurafenib + cobimetinib compared with vemurafenib and with dabrafenib for patients with advanced melanoma.

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of vemurafenib + cobimetinib is compared with vemurafenib and with dabrafenib in patients with advanced melanoma and the BRAF-mutation.

4.2 Company's review of published economic evaluations

A systematic search of the literature was conducted by the company to identify economic evaluations of cobimetinib for patients with advanced (unresectable or metastatic) BRAF V600 mutation positive melanoma. See section 3.1 of this report for the ERG critique of the search strategy.

The inclusion and exclusion criteria for the systematic review are listed in Appendix 9 of the CS, page 223. The inclusion criteria state that full economic evaluations of BRAF inhibitors (cobimetinib in combination with vemurafenib compared to any other BRAF inhibitor) would be included. The exclusion criteria state that studies that only considered V600 mutation-negative melanoma would be excluded.

Eight studies were identified from screening 114 titles and abstracts. All eight studies were excluded, as none included cobimetinib. No studies therefore were included for full review.

The ERG found one study that compared the clinical effectiveness and cost effectiveness of seven drugs used for the treatment of advanced melanoma in the Norwegian setting[35]. The drugs included cobimetinib, dabrafenib, vemurafenib, ipilimumab, nivolumab, pembrolizumab and trametinib. The study conducted a systematic literature review and compared treatments with NMA using direct and indirect evidence with dacarbazine as a common comparator. The study conducted a probabilistic discrete-time Markov cohort model to compare the cost effectiveness of the treatments over a 10 year time horizon with monthly cycles. Excluding those treatments not included within the scope of this appraisal, vemurafenib was dominated and the ICER of vemurafenib + cobimetinib compared to dabrafenib was 2,837,207 NOK (Norwegian Krone) (£234,000 per QALY).

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

The ERG considered the NICE reference case requirements during the critical appraisal of the submitted economic evaluation (Table 17).

Table 17 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	CS Table 1, page 17
Comparator: As listed in the scope developed by NICE	Yes	Consistent with NICE scope but does not include immunotherapies which have been recommended for this patient group.

Perspective on costs: NHS and PSS (personal social services)	Yes	
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	?	Cost utility analysis. Results not presented incrementally for all comparators, rather separate analyses are presented for the intervention compared to vemurafenib and dabrafenib.
Synthesis of evidence on outcomes: Based on a systematic review	Yes	Inclusion criteria reported in CS Table 6, page 38.
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	30 year time horizon
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	Yes	QALYs are used in the analysis. EQ-5D-5L used from the coBRIM trial for PFS and standard gamble used for progressed disease from Beusterien et al.[36]
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	?	Patients from the coBRIM trial completed EQ-5D for PFS, but general public sample estimated utility directly for progressed disease.
Source of preference data: Representative sample of the UK population	?	The EQ-5D values are derived using a Crosswalk study of which a small sample are from the UK.
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	

Notes: ? = uncertain; N/A=not applicable

In general, the company model is in line with the NICE reference case. However there are two aspects to note: firstly, the company has not presented a fully incremental analysis, rather, pairwise analyses have been presented for vemurafenib + cobimetinib compared to

vemurafenib and to dabrafenib; secondly, the source of quality of life used for patients with progressed disease is not in line with the NICE reference case.

4.3.2 Model Structure

The company developed a partitioned survival model with three health states: progression-free survival (PFS), progressed disease (PD) and death. A schematic of the company's model is presented in Figure 6. The model was developed in Microsoft Excel with a 1-week cycle length. Costs, QALYs and life years were presented as outputs of the model. The CS states that the model takes the perspective of NHS England and PSS. The time horizon is set at 30 years and the CS states that this is consistent with prior melanoma appraisals and appropriate for the average age of patients in the model (CS Table 45). Both costs and outcomes are discounted at 3.5% per annum, as recommended by the NICE Methods Guide for Technology Appraisals.[37]

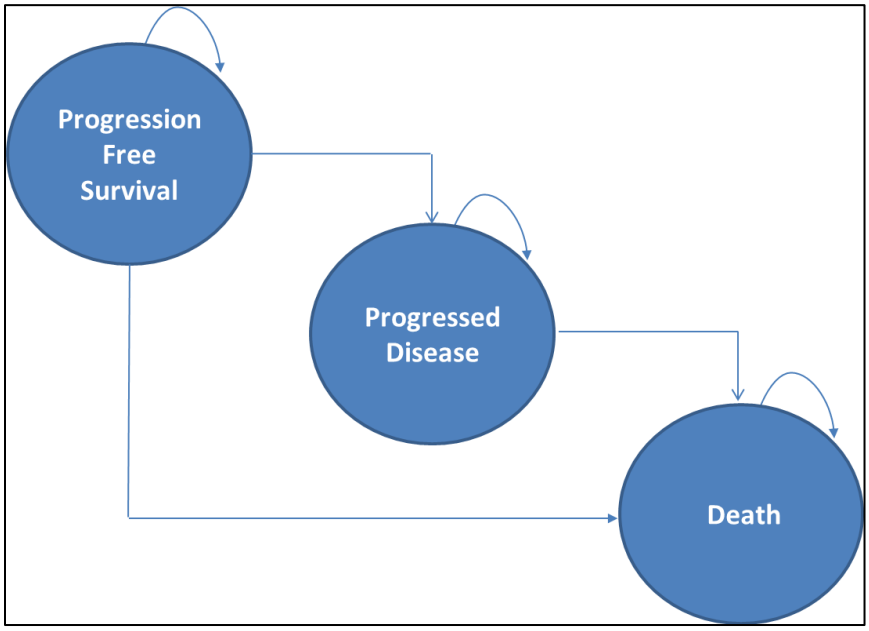


Figure 6 Schematic of the company's economic model (CS Figure 15)

All patients enter the model in the PFS state. Patients progress to the death state according to an estimate of OS from the coBRIM trial and the number of patients remaining in the PFS state is determined by the PFS estimated from the coBRIM clinical trial. The number of patients in the progressed states is then calculated as the difference between the PFS and OS curves. Patients remain on treatment whilst they are in the PFS health state, as per the marketing authorisation for vemurafenib and cobimetinib. Treatment duration is taken from the time on treatment data from the coBRIM study. The model assumes no subsequent lines of anti-cancer

therapy, following progression on the intervention or a comparator. The CS states that there is a lack of data to allow modelling of subsequent treatments. Furthermore, the CS states that the frequency and type of subsequent treatments did not differ by trial arm in coBRIM and that this approach is consistent with prior melanoma technology appraisals. The ERG considered that this was a reasonable approach and that the exclusion of subsequent treatments is unlikely to have an impact on the model results as the time spent in the progressed disease state is similar in all treatment arms. We conduct an illustrative scenario that shows the impact of including subsequent treatment in the economic model in section 4.4.

The CS justifies the model structure and health states by stating that they are closely aligned with the clinical pathway (NICE Melanoma Pathway) and are consistent with approaches taken in earlier technology appraisals for metastatic melanoma (TA269,[26] TA319, [6] TA321,[7] TA366[9]) The ERG agrees that the approach taken and structure adopted is appropriate for the disease pathway. Furthermore the ERG suggests that a survival model is an intuitive structure as it directly utilises the clinical trial survival data. The ERG also considers that the time horizon chosen is appropriate as only a small proportion of patients would still be alive after 30 years (~5% of patients).

4.3.3 Population

The economic model includes treatment-naïve adult patients with unresectable or metastatic BRAF600 mutation positive melanoma. The characteristics of the patients in the model are based upon the patients in the coBRIM trial and are described in CS Table 14. The CS states that the coBRIM study included a small number of UK patients (n=29 from 11 centres) and that the outcomes seen from the study are expected in UK patients (CS Table 45). Expert clinical advice to the ERG was that the patients in the coBRIM trial are similar to those seen in the UK. The patient population is consistent with the marketing authorisation and the population specified in the NICE scope.

4.3.4 Interventions and comparators

The economic model provides two separate analyses: i) vemurafenib + cobimetinib compared to vemurafenib and ii) vemurafenib + cobimetinib compared to dabrafenib. These comparators correspond to NICE's scope. The interventions are implemented in the model in accordance

with their current marketing authorisation and doses (see section 4.3.7). The ERG notes that other potential comparator melanoma treatments have not been included within the NICE scope, for example ipilimumab and pembrolizumab. These are now recommended by NICE to treat advanced melanoma, including BRAF mutation positive melanoma and we have been advised that these treatments are often prescribed for BRAF mutation positive melanoma patients. The ERG also notes that an alternative BRAF inhibitor and MEK inhibitor combination therapy, dabrafenib + trametinib, is currently being appraised by NICE in a separate technology appraisal (ID661).

4.3.5 Treatment effectiveness and extrapolation

For the comparison between vemurafenib + cobimetinib and vemurafenib, the clinical effectiveness estimate is based upon the survival curves from the coBRIM trial. For the comparison between vemurafenib + cobimetinib and dabrafenib, an indirect treatment comparison was conducted via an NMA and the inverse AFT values were applied to the vemurafenib + cobimetinib survival curves to obtain the survival curve for dabrafenib. As discussed earlier in this report (Section 3.1.7), the ERG considered the NMA to be comprehensive in terms of its search for relevant studies, but was limited by a small number of included trials, and uncertainties about heterogeneity between the trials in potential effect modifiers.

4.3.5.1 Progression free survival (PFS)

The company fitted parametric distributions to the observed PFS from the coBRIM trial. The log-logistic, Weibull, lognormal, gamma, Gompertz and exponential distribution were assessed using the Akaike Information Criterion (AkIC), Bayesian Information Criterion (BIC) and visual assessment of each fitted curve against the observed data. The company considered the log-logistic distribution to be the most appropriate based upon AkIC, BIC and visual inspection. The fitted PFS data for both treatment arms compared to the observed data is shown in Figure 7. Alternative distributions are shown in CS Appendix 10 and model results using these distributions shown in Table 27 of the ERG report. The company further justifies the use of the log-logistic by demonstrating that the log-logistic assumption is satisfied (CS Figure 17). It is also possible to use the KM data with a fitted parametric curve. The CS does not report the results from these analyses but the ERG observes that for each parametric distribution, there

was little difference in the results from using a parametric distribution for the whole survival curve or using the KM data with the parametric distribution for the tail.

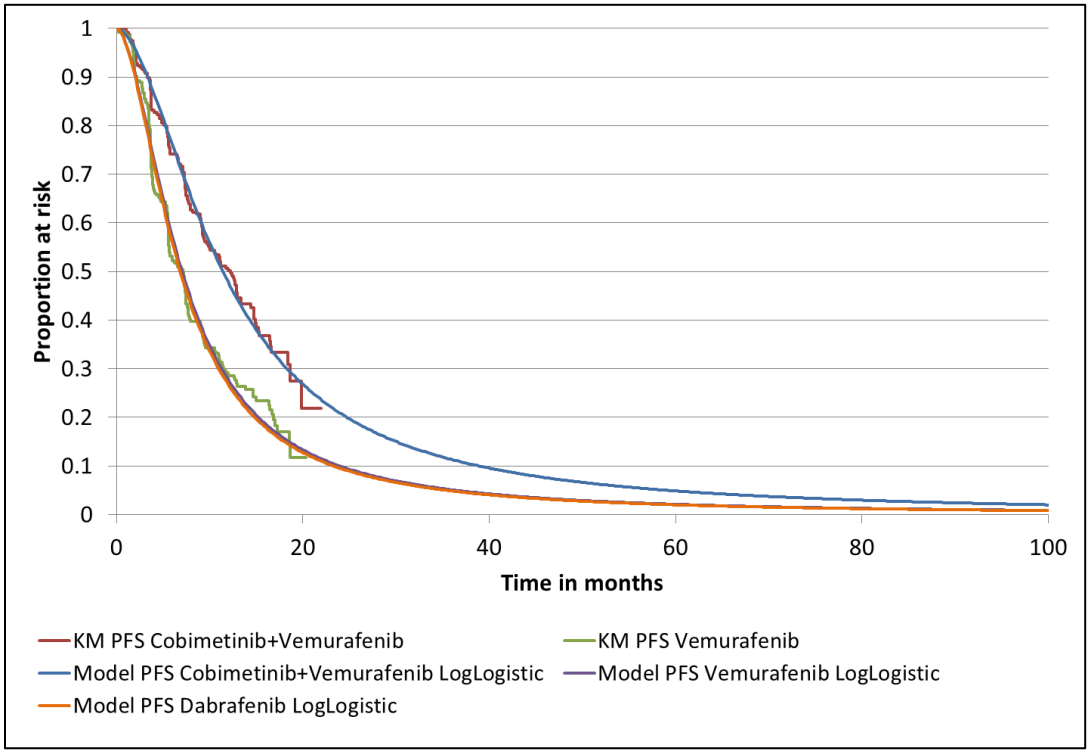


Figure 7 PFS observed data from coBRIM trial and the Log-logistic fitted curves used in the economic model (CS Figure 16)

The ERG considers that the company's choice of parametric distribution is reasonable and provides a good fit to the trial survival data based upon AkIC/BIC and visual interpretation (Figure 7). In addition, the long-term extrapolation appears to be similar to that seen in a phase I trial of vemurafenib where 3 out of 48 patients (6%) were treated for more than four years.[38] We agree that the conditions required for the use of the log-logistic distribution have been satisfied. Furthermore we consider that the lognormal and gamma distributions would produce a similar fit to the log-logistic and result in higher ICERs for vemurafenib + cobimetinib vs vemurafenib of between £157,377 and £164,485 per QALY respectively. The differences between these PFS curves is small and therefore, given the uncertainty in extrapolating beyond the trial data, the ERG considers both these curves would also be a reasonable choice for PFS.

The NMA used the AFT model in preference to a PH model. The ERG's critique of this approach is in section 3.1.7. The PFS for vemurafenib + cobimetinib was adjusted according to

the inverse AFT for the PFS curve for dabrafenib. The inverse AFT results for vemurafenib + cobimetinib vs. dabrafenib were 0.599 (95% CrI 0.47, 0.86) for PFS.

4.3.5.2 Overall survival (OS)

Extrapolation of the OS curve beyond the observed coBRIM trial data was a two stage process. Firstly, the survival data were adjusted, using a 'mixture cure rate methodology', assuming that a small proportion of patients had a low risk of cancer-related death. Secondly, parametric models were fitted to the adjusted trial data.

The CS assumes that the risk of death for patients with metastatic melanoma declines with time, with the risk inversely proportional to the time since diagnosis. The CS cites evidence from the US Surveillance, Epidemiology, and End Results (SEER) cancer registry[39] that shows this decline in risk over time (CS Figure 19). Furthermore, the CS notes that prior NICE melanoma appraisals (TA357[10] and TA366[9]) have also included this assumption.

Using a mixture cure-rate methodology, the overall risk is estimated by combining (via a weighted average) the risk for patients with low risk of cancer related death and those with high risk of cancer related death.

The trial population survival is expressed as S(t),

$$S(t) = S_b(t)\pi + (1-\pi)S_b(t)S_c(t)$$

where the 'cure fraction' is expressed as π, the patients at high risk of cancer-related death [$S_c(t)$], and the patients at low risk [$S_b(t)$].

The 'cure fraction' represents the proportion of patients for whom their disease is stable and the risk of death attributable to cancer is equal to their risk of death from other causes. Therefore the risk of death for these patients is assumed to be the same as for the general population.

The cure fraction is estimated using data from the SEER registry. The resulting cure fraction is [redacted] The OS curves fitted to coBRIM trial data with and without the cure rate for patients treated with vemurafenib is shown in Figure 8.

The median OS follow-up for the coBRIM trial was 18 months. The ERG was unable to find any longer term studies for patients treated with vemurafenib + cobimetinib. The ERG identified a

study by Puzanov and colleagues[38] that reported 4 year melanoma specific survival rate in patients treated with vemurafenib. The ERG has compared data from this study with the base case OS from the company's model for vemurafenib (which includes the cure rate), as seen in Figure 8. From a visual inspection of this figure, the ERG suggests that this study supports the use of a cure rate and the OS curve from Puzanov and colleagues[38] is seen to be similar to that used in the company's model.

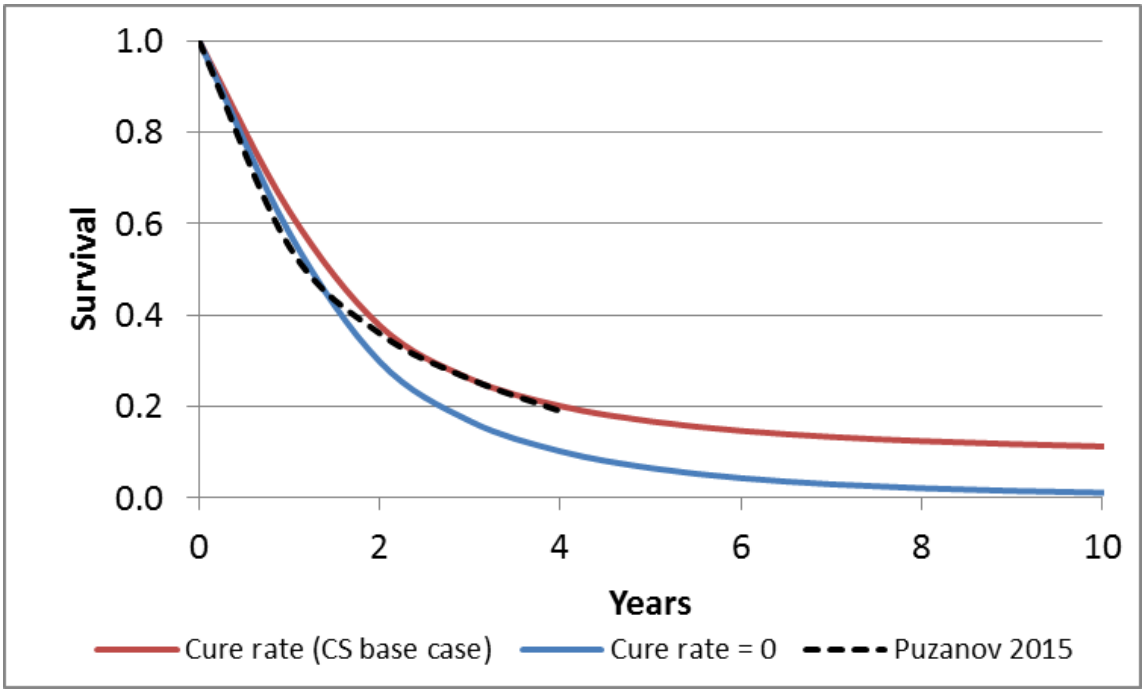


Figure 8 OS for the economic model and Puzanov et al study for patients treated with vemurafenib

The company fitted exponential, Weibull, log-logistic, lognormal, Gompertz, gamma and generalized gamma distributions to the trial arms of the coBRIM trial. The parametric models incorporated the cure function. According to the AkIC / BIC, the [redacted] distribution was selected as the most appropriate fit. The CS presents the fit for the lognormal distribution in CS Figure 23 (see **Error! Reference source not found.** below) and the fit for the other distributions in Appendix 10. The company conducted sensitivity analyses using the alternative distributions (CS Table 60). The model results are sensitive to the parametric distribution chosen and the ICER varies up to £253,766 per QALY for the Gompertz distribution for vemurafenib + cobimetinib compared to vemurafenib (Table 26).

The OS for vemurafenib + cobimetinib was adjusted according to the Inverse AFT for the OS curve for dabrafenib. The inverse AFT results for vemurafenib + cobimetinib vs. dabrafenib were 0.635 (95%CrI 0.46, 0.77) for OS.

The ERG considers that the company's choice of parametric distribution is reasonable and provides a good fit to the trial OS data based upon AkIC/BIC and visual interpretation (CS Figure 23). The ERG considers that the log-logistic distributions would also produce a similar fit to the [redacted]. In addition, the company provides an option for analyses using the KM trial data with a fitted tail. For this option, the KM data are used for the period until the time at which 20% of patients were still at risk, and then the fitted parametric curve is used thereafter We consider that using the KM data with a fitted [redacted] tail would also be a reasonable approach and results in a higher ICER of £176,358 per QALY.

4.3.5.3 Time on treatment

Patients are treated until disease progression or unacceptable toxicity for both cobimetinib and vemurafenib, as per their marketing authorisations. The CS stated that as a small proportion of patients discontinued treatment due to AEs or toxicity, the actual treatment duration in the trial is

shorter than the time until disease progression (CS Table 45). The model analysis for vemurafenib + cobimetinib compared to vemurafenib uses the treatment duration observed in the coBRIM trial. The company fitted parametric curves to the time on treatment distributions observed in the coBRIM trial for vemurafenib + cobimetinib and vemurafenib treatment arms. Visual inspection of the fitted curves indicated that the parametric distributions were a poor fit for the beginning of the KM data and the company therefore used the KM data in the model with a parametric tail. According to the AkIC and BIC treatment values, the Weibull provided the best fit for both cobimetinib and vemurafenib in the treatment arm and the log-logistic was the best fit to the vemurafenib arm. Parametric curves were fitted from month 15 in both the intervention and comparator arms, based on the time point at which 20% of patients were still at risk.

The ERG notes that the company used different parametric curves for the intervention and comparator arms and this choice causes a convergence in the TOT curves for the intervention and comparator arms which favours the vemurafenib + cobimetinib (Figure 9). The ERG considers it is more reasonable to use the log-logistic parametric curve for both the intervention and comparator (Figure 10). Furthermore, this would also be consistent with the choice of the log-logistic distribution for the PFS curve. The ERG investigates the use of using the KM data with a log-logistic tail for both the intervention and the comparator arm results in Section 4.4.

For the comparison with dabrafenib, PFS was used for a proxy for time on treatment for the vemurafenib + cobimetinib and dabrafenib treatment arms. The company justifies the use of PFS as a proxy for TOT for dabrafenib by stating that there was an absence of available data for this comparator. Using this approach gives higher treatment costs for this comparison compared to the comparison between vemurafenib + cobimetinib and vemurafenib. For this reason the company presents two pairwise comparisons between vemurafenib + cobimetinib compared to vemurafenib and dabrafenib, rather than a fully incremental analysis.

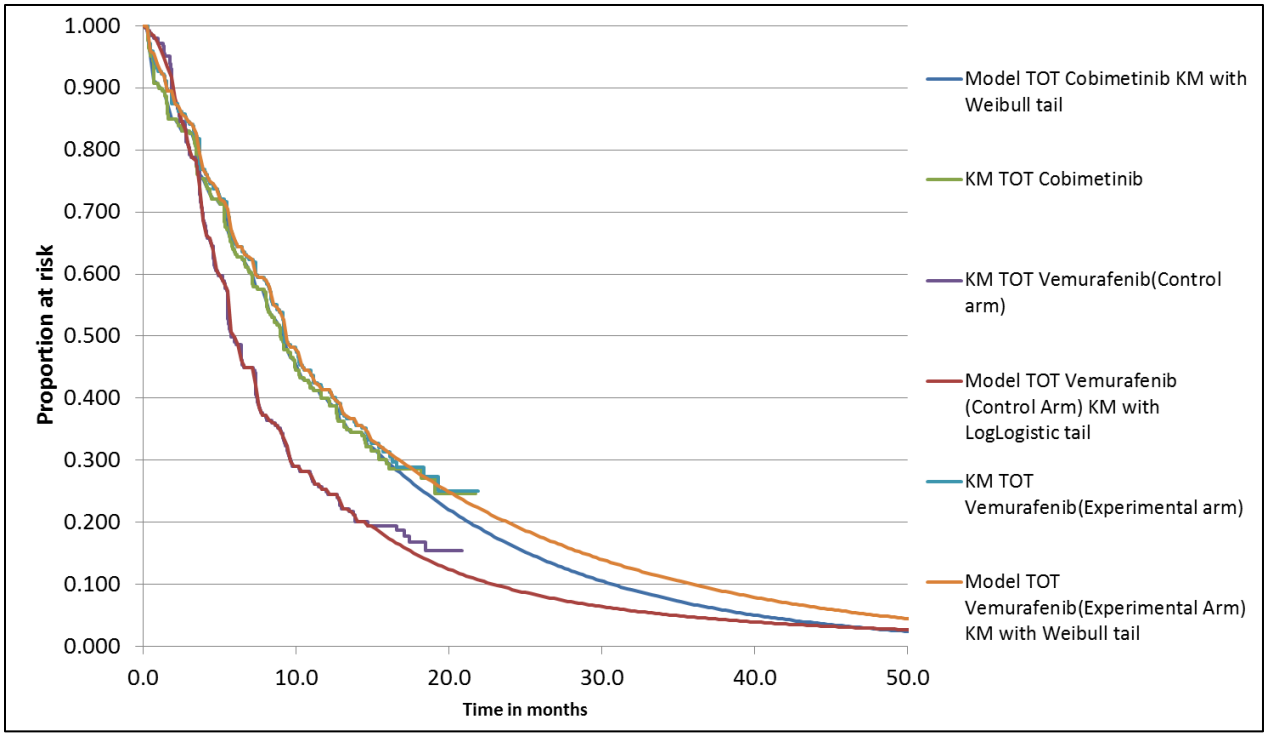


Figure 9 TOT for the economic model using the company base case parametric curves (CS Figure 26)

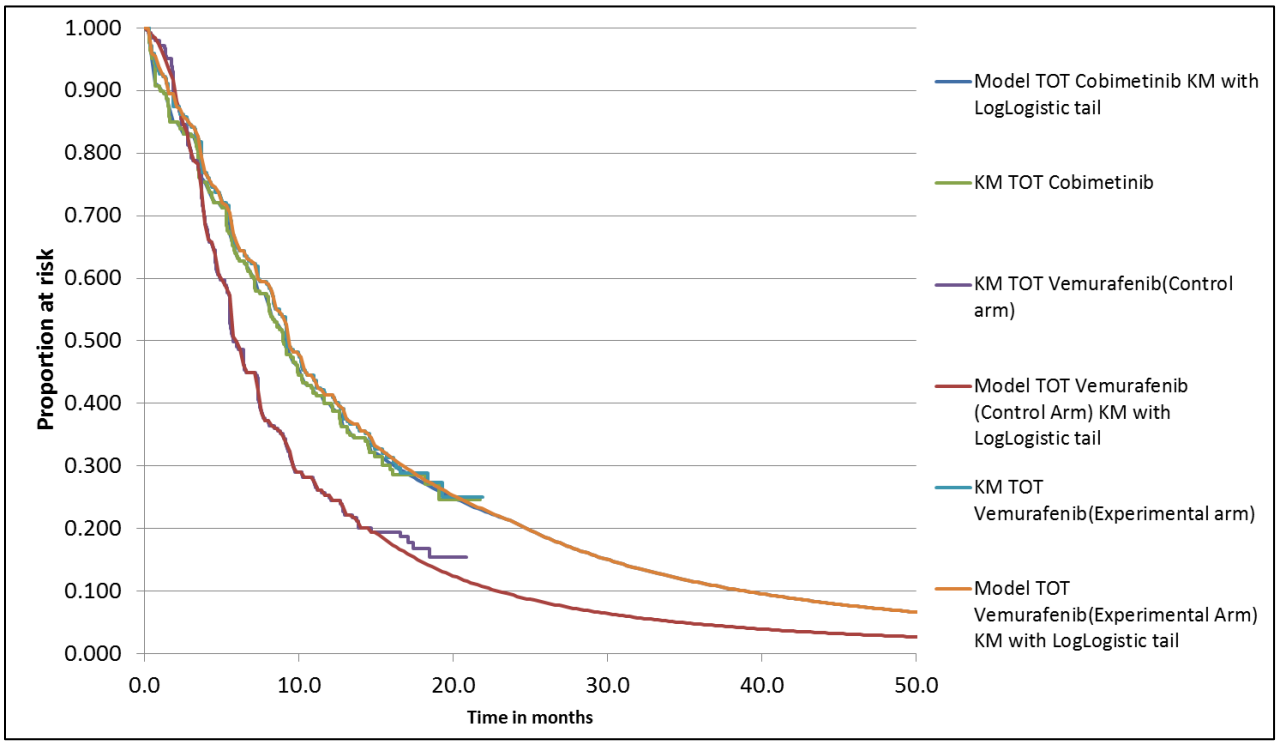


Figure 10 TOT for the economic model using the KM log-logistic parametric curve for the vemurafenib + cobimetinib treatment arm

4.3.5.4 Adverse events

The CS model includes AEs for grade 3 or 4 at an incidence of 3% or more from the coBRIM trial for the vemurafenib + cobimetinib and vemurafenib arms. The incidence of the AEs is shown in Table 14 (CS Table 23). The costs of treating AEs have been included in the economic model. More details on the AEs in the coBRIM trial are given in Section 3.3.6.

4.3.6 Health related quality of life

HRQoL outcomes were quantified in the cost-effectiveness model by assigning utility weights to the two alive-states of the decision model (PFS and PD), a method that is commonly used in cancer models. Whilst for PFS, HRQoL weights were estimated directly from patient data collected within the coBRIM trial, the HRQoL weights for the PD state were from the literature. The HRQoL values used in the model are shown in Table 18.

Table 18 Summary of utility values for the company's economic model (adapted from CS Table 36)

State	Utility value: mean (standard error)	95% confidence interval	Source of utility data
PFS (vemurafenib + cobimetinib)	0.837	0.830, 0.844	coBRIM trial
PFS (vemurafenib)	0.819	0.812, 0.827	
PFS (dabrafenib)	0.819	0.812, 0.827	Assumed to be equivalent to vemurafenib arm of coBRIM trial
PD <5 years	0.590	0.578, 0.602	Literature review (Beusterien et al., 2009)[36]
PD ≥5 years	0.770	0.755, 0.785	

4.3.6.1 Individual patient data collection for HRQoL within the coBRIM trial

PFS was the primary endpoint of the coBRIM study, but HRQoL-outcomes were collected as secondary end points using both the EORTC QLQ-C30 and EQ-5D-5L instruments. The EORTC QLQ-C30 is a cancer specific HRQoL questionnaire which consists of 30 questions with a 4-point response format, moving from "not at all" to "very much".[40] The generic EQ-5D instrument was used in its 5-level format, and both questionnaires were administered in local language on the first day of cycle 1 before initiating treatment and at each study visit before undertaking any further study related assessments[12]. Whilst for PFS, total observations reached 1323 in the vemurafenib + cobimetinib and 1103 in the vemurafenib + placebo group,

observations in the progressed disease state are scarce, with only 57 in total. It is not clear how observations from individual patient data were pooled to estimate state weights for HRQoL, whether results were properly adjusted for baseline utility in both arms of the trial, nor whether observations for some patients were missing, and if so, how missing data were handled.

4.3.6.2 Systematic review of relevant HRQoL literature

As stated in Section 3.1.1 of this report, a systematic literature review was conducted by the company in March 2015 and updated in December 2015 in order to identify health state utility weights for patients with advanced (unresectable or metastatic) melanoma. The initial search was not restricted by intervention, study design, country, or date and aimed at identifying studies published in English language which reported utility weights elicited through time trade off (TTO), standard gamble (SG), generic preference-based HRQoL instruments or mapping studies which allow cross-walking towards such generic preference-based measures for patients with advanced melanoma. It is not clear whether any measures to assess study quality were applied, but accordance with the NICE reference case was explicitly assessed. The literature search identified 17 papers, and the CS states that six of these 17 studies reported health state utility weights using the EQ-5D. However, the CS states that none of these 6 studies were deemed appropriate to estimate health state utility weights for the economic model as the reported EQ-5D data were related to different pharmacological treatments for melanoma (rather than the treatments in this appraisal) or the treatment was not reported. The CS further states that data from five of the six publications reporting EQ-5D utilities were not consistent with the NICE reference case (or information was limited so that it was not possible to assess this). Nevertheless, the SLR also identified a study by Beusterien and colleagues [36] which has been used previously to estimate utility weights in the technology appraisal on vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (NICE TA269),[26] This study has subsequently been used to estimate utility weights for the PD state of the model.

4.3.6.3 Utility weights for progression free survival (PFS)

For the PFS state of the model, patient-level EQ-5D-5L data from the coBRIM study were used to estimate utility weights. The recently developed EQ-5D-5L has advantages over its 3L predecessor as it is deemed more responsive to changes in health status and avoids ceiling or floor effects which have been observed in the 3L version.[41] However, in order to use the EQ-5D

5L data from the coBRIM trial in the economic model, it was necessary to obtain respective health state utility weights. Two previously validated methods were used for obtaining such utility weights: first, a crosswalk method[41] to estimate utility values for the EQ-5D-5L from available 3-level general population value sets; and second, an algorithm developed by the Office of Health Economics (OHE)[42] which utilised both TTO and discrete choice experiments (DCE) in order to estimate EQ-5D-5L utility weights for the general population in England.[42] Resulting utility weights from both methods were then discussed with expert advisors, and subsequently those relating to the OHE algorithm were dropped for the base case but tested in scenario analysis as they were deemed unrealistically high by experts and exceeded average population norms for the equivalent age group of the coBRIM trial. The ERG believes that the approach taken by the sponsor is reasonable and well justified. Though the OHE dataset is now validated and endorsed by the EuroQoL Group to obtain EQ-5D 5L weights for England, these values are not consistent with EQ-5D 3L weights used in previous technology appraisals. Further, though not clearly stated in the CS, it is reasonable to assume that the crosswalk values are UK specific as the converter used by the sponsor allows estimation of UK specific EQ-5D 3L utility weights from available EQ-5D 5L data. Therefore, using the crosswalk method to obtain equivalent 3L values so to ensure comparability with other technology appraisals in the base case and testing OHE values as a form of scenario analysis is a reasonable approach taken in the CS.

Adverse events were not explicitly accounted for when estimating utility weights for the PFS state of the model. Rather, as all utility values were estimated directly from individual patient data obtained within the coBRIM trial, any AEs are assumed to be reflected in the observed utility values. The ERG believes that this assumption is reasonable given the nature of the data available, but it does not allow explicit assessment of disutility from AEs within the economic model. This is of particular importance as the utility weight for the vemurafenib + cobimetinib group (0.837) was higher compared to the vemurafenib or dabrafenib group respectively (0.819).

Though the ERG agrees with the CS that utility weights for PFS (Table 18 above, CS Table 36) are broadly similar to previous NICE technology appraisals for melanoma (Table 19, CS Table 35), particular concerns relate to the difference in utility weights between intervention and comparator arms.

Table 19 Comparison of utility values from prior NICE technology appraisals relevant to scope population (CS Table 35)

	Drug					
Health state	**Vemurafenib**	**Dabrafenib**	**Ipilimumab**	**Pembrolizumab**	**Nivolumab**	**Cobimetinib +vemurafenib**
PFS	0.85	0.77	-	-	-	0.832
PD	0.59	0.68	-	-	-	0.798
PFS≥ 30 days					0.8018	
PFS< 30 days					0.7795	
PD≥ 30 days					0.7277	
PD< 30 days					0.7054	
12+ months until death			0.885	0.82		
9-12 months until death			0.880	0.71		
6-9 months until death			0.854	0.66		
3-4 months until death			0.810	0.66		
1-3 months until death			0.739	0.57		
<1month until death			0.631	0.33		

According to the CS, the HRQoL for patients in the PFS state for vemurafenib + cobimetinib is higher than for those patients receiving vemurafenib or dabrafenib (Table 18). A potential justification could be, for instance, that AEs are generally lower in the combined treatment group, which would then lead to higher HRQoL for these patients in PFS. However, this is neither confirmed through the data reported on AEs in the coBRIM trial nor was the disutility from adverse events explicitly assessed in the CS which makes any assessment of potential reasons for the difference in utility weights by the ERG uncertain. In addition, the CS does not provide details on the statistical methods used to calculate HRQoL weights from patient data or the frequency or handling of missing values. For instance, if values are not missing at random, this could already explain why the HRQoL weight in the combined treatment group was found to be higher compared to the vemurafenib arm of the coBRIM trial. The ERG therefore suggests re-running the model with identical HRQoL values for PFS across the three therapies under assessment, for example by using the HRQoL weight estimated for vemurafenib from patient

data in the coBRIM trial (0.819). The ERG has conducted this as a scenario analysis in Section 4.4.

4.3.6.4 Utility weights for the progressed disease (PD) state

Patient data from the coBRIM trial was scarce for PD, due to the fact that observations are only available until 12 weeks after the end of treatment. Consequently, utility weights for the PD state in the model are based on a published study by Beusterien and colleagues.[36] This study was identified through the systematic literature review on HRQoL as summarised above, and it has been used to estimate state weights in a previous technology appraisal for vemurafenib by the same company (NICE TA269).[26]

The study by Beusterien and colleagues[36] elicited utilities from 140 respondents in the UK (n = 63) and Australia (n = 77) related to advanced melanoma whilst explicitly capturing both intended clinical response and unintended toxicities related to treatment. Standard gamble was used to elicit utilities and the study sample was recruited from the general population. The authors estimated utilities for four different clinical response states (partial response (0.85); stable disease (0.77); progressive disease (0.59); and best supportive care (0.59)).

The utility weight for progressive disease (0.59) was then used for the PD state in the model without taking into account utility decrements from toxicities. This assumption is reasonable as treatment should have discontinued when patients enter the PD state. Further, the utility weight for stable disease (0.77) was applied to patients in the PD state for more than 5 years, which follows the assumption that patients with long term survival have a higher HRQoL as their disease state has stabilised. The same assumption has been made in a previous technology appraisal on vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (NICE TA269).[26] In addition, different AEs from toxicities were assessed and estimated as utility decrements.

The ERG has some concerns with respect to the choice of the study by Beusterien and colleagues[36] to estimate utility weights for the PD state of the model. Both the method used in this study (standard gamble), which is choice based, and a sample for valuing health states, which was taken from the general public, accord with the NICE reference case. However, according to the reference case, the actual assessment of health states should be based on patients, and this was not the case in the study by Beusterien and colleagues. Further, a later

appraisal of nivolumab for patients with advanced (unresectable or metastatic) melanoma (NICE TA384)[4] used higher utility values for progressed disease (CS Table 35). In this appraisal, utility weights were estimated from patient-level observations on EQ-5D from the CheckMate 066 trial.[43] EQ-5D data from 1540 visits involving 362 study patients was used to estimate health state utility weights for both pre-progression and post-progression, and in each state for patients being either more or less than 30 days from death. Utility weights for progressed disease were estimated as 0.7277 for patients ≥30 days from death and 0.7054 for patients <30 days from death respectively. The ERG believes that this study may be more in accord with the NICE reference case as the EQ-5D was used in a patient population with advanced (unresectable or metastatic) melanoma. Accordingly, the ERG suggests using alternative utility weights for PD in a scenario analysis using the weights from the NICE TA384 on nivolumab. The ERG has done this scenario analysis in Section4.4.

4.3.6.5 Bottom-line summary of ERG view on utilities

The ERG has several concerns related to the utility weights used in the model by the CS. For PFS, it is not clear why utility weights for combined therapy are higher compared to vemurafenib or dabrafenib only. Fewer AEs from toxicities in the combined treatment arm may be a potential reason, but this cannot be confirmed by the data on AEs reported from the coBRIM trial. The lack of reporting of statistical methods to estimate utility from the data and the existence and handling of missing values make it impossible to assess potential reasons for higher utility weights in the combined treatment arm of the coBRIM trial. The ERG therefore suggests a scenario analysis using identical utility weights in PFS for combined therapy and monotherapy with vemurafenib or dabrafenib respectively.

The ERG has further concerns regarding the utility weight for PD as taken from Beusterien and colleagues.[36] This study does not accord the NICE reference case as health states were assessed from a general public sample, and TA 384 estimated higher utility weights in PD using EQ-5D for patients with advanced (unresectable or metastatic) melanoma. The ERG therefore suggests scenario analysis using a utility weight of 0.77 for PD as taken from NICE TA384.

4.3.7 Resource use and costs

Costs considered in the model include drug cost and administration costs, treatment of AEs, weekly supportive care (health state cost), and diagnostic costs. Drug costs are based on

published list prices, assumptions about existing patient access schemes and average doses taken by patients observed in the coBRIM trial. Administration costs were estimated in accordance with previous technology appraisals for vemurafenib and dabrafenib (NICE TA269;[26] TA321[7]). The cost of AEs was estimated from different sources, including previous technology appraisals and Healthcare Resource Groups (HRG) reference cost (unit cost estimates). Weekly supportive care (health state cost) were taken from a published study[44] which was identified through a systematic literature review on cost and resource use for advanced (unresectable or metastatic) melanoma, and this estimate was also consistent with previous technology appraisals (NICE TA269;[26] NICE TA319;[6] NICE TA357 [10]). Finally, diagnostic costs were estimated in accordance with the prior vemurafenib technology appraisal (NICE TA269[26]), and these costs were applied both to the intervention and both comparators.

4.3.7.1 Systematic literature review to identify resource use and unit cost estimates

The company conducted a systematic literature search to identify resource use and unit cost estimates for the model (see Section 3.1.1). Studies were included if they were published in English language between 1st January 2000 and 9th December 2015, and only if they reported on resource use or cost drivers related to advanced (unresectable or metastatic) melanoma. No restriction was placed on country or study design, though papers in which the economic perspective was unclear were excluded. Studies were also excluded if they related to early stage melanoma or reported on indirect costs (such as productivity costs) only.

The systematic review identified only two relevant papers for estimating resource use and unit costs for the model. One was a published study[44] and one a conference poster.[45]

Johnston and colleagues[44] performed a retrospective analysis of hospitalisations, hospice care, and outpatient visits recorded during a multinational observational study (the MELODY study). The aim was to assess resource utilisation and costs in patients with advanced melanoma (stage III or IV) who either received active treatment or best supportive care. Patients from the UK, Italy, and France were recruited between July 2005 and June 2006 and medical records were used to assess patient and disease characteristics, treatment patterns, respective outcomes and resource use from the time of diagnosis until May 2008 or until the patient had died. Resource use data were then multiplied with national unit cost estimates to calculate per patient cost from a UK NHS perspective. Unit cost data referred to the year 2009.

The study by Vouk and colleagues[45] also took a UK NHS perspective, and reported on the economic burden of adverse effects associated with metastatic melanoma treatment. Based on a literature review, 29 AEs with all severity grades were selected. Associated resource use was then estimated through a Delphi panel consisting of 4 clinicians, and unit costs (2011-2012) were obtained from the literature to estimate the cost per event per patient.

4.3.7.2 Drug acquisition costs

Drug acquisition costs in the model consist of drug cost and administration cost. For vemurafenib + cobimetinib, weekly drug costs were estimated from published list prices and the actual dose taken by patients within the coBRIM trial. Due to dose modification, this dosage was generally lower than the label dose, and clinical advisors were consulted to judge whether observed doses are likely to match those used in clinical practice. The costs in the model are based on the list price in the base case with further analyses including the confidential PAS which exists for dabrafenib and vemurafenib. The drug cost assumed in the model are summarised in Table 20 below.

In contrast to the above, the cost for dabrafenib was estimated from the label doses. The company justified this assumption by stating that the coBRIM trial did not include dabrafenib so that actual doses could not be estimated. However, the ERG believes that this is an inconsistency which may bias results of the economic model. To be consistent, one could either use label doses to estimate weekly drug cost for all three treatments, or estimate drug cost for dabrafenib with modified doses. The ERG has tested these scenarios in Section 4.4.

Table 20 Weekly vemurafenib + cobimetinib drug costs at according to average dose taken in coBRIM study & weekly dabrafenib cost based on label doses.

	Daily dose according to label dose	Actual dose taken in coBRIM trial	Per cycle cost (week)
Cobimetinib	3 tablets of 20 mg days 1 - 21 of a 28 day treatment cycle	2.602 tablets per day	£1236*
Vemurafenib + cobimetinib	8 tablets of 240mg	7.062 tablets per day	£1545
Vemurafenib	8 tablets of 240mg	6.99 tablets per day	£1529
Dabrafenib	150mg twice daily (equivalent to a total daily dose of 300 mg)	75mg x 28 = £1400	£1400

*during treatment periods only

Besides dosage and prices, another important factor to estimate drug cost in the model is the time on treatment. In general, time on treatment was assumed to last until disease progression or until toxicity reaches an unacceptable level. The company's approach to estimating time on treatment is discussed earlier in Section 4.3.5.3.

Finally, a pharmacy charge of £13 was applied to both the intervention and each comparator respectively to reflect administration cost for each 28 day cycle of therapy. The ERG agrees that this approach is consistent with previous STAs and reasonable given that all drugs under assessment are oral products which do not require access to a chemotherapy suite and only have to be dispensed by a pharmacist once per cycle.

4.3.7.3 Health state cost (weekly supportive care)

The company used data from the study by Johnston and colleagues,[44] which was identified in the systematic review described above. This study has also been used as a basis for estimating health state cost in a number of previous NICE STAs (TA269;[26] TA319;[6] TA357;[10] and TA366 [9]). In line with these technology appraisals, the company therefore set monthly cost of best supportive care for both PFS and PD at £378 (£87 per week). The ERG believes that this approach is generally reasonable and justified for the base case analysis, especially as the same health state cost was assumed for the intervention and comparator technologies. We consider there is also reason to believe that health state costs reduce in patients with long term stable disease. The ERG has investigated the use of lower health state costs for progressed disease by using the values shown in CS Table 41 from discussion with clinical experts (PD year 1 £87.23/week; PD year 2-3 £20.25 / week; PD year 4-6 £12.17/week; and PD year 6+ £6.51/week) and found that using these values has a minimal impact on the model ICERs.

4.3.7.4 Adverse events costs

The coBRIM trial was used for combination therapy and vemurafenib monotherapy for estimating cost related to the treatment of AE, incidence data from. Unit costs were used from prior STAs or from HRG unit cost (2014-15)[46] for valuing the resource use associated with treating AEs. Only AE with an incidence of at least 3% and grades 3 or 4 were considered for the economic model. The study by Vouk and colleagues,[45] which was included in the systematic review, was not used for the model as the sponsor deemed treatments considered there not specific enough to match either the intervention or comparator.

Table 21 (CS Table 43) summarises AEs with their respective cost assumed in the economic model.

Table 21 List of adverse events and summary of costs in the economic model

Adverse reactions	Items	Value	Reference in submission
Liver function test abnormality*	Outpatient cost, % No treatment, % Mean cost per patient	£158.54, 20% £0, 90% £31.71	HRG service code 370, medical oncology
Arthralgia	Outpatient cost	£139.52	HRG service code 191, pain management
Basel cell carcinoma		£198.66	JC41Z: outpatient major skin procedure
Diarrhoea	Inpatient cost, %	£838.46, 50%	TA366 2015
	Outpatient cost, %	£144.05, 50%	TA366 2015
	Mean cost per patient	£491.26	TA366 2015
Fatigue	Inpatient cost, %	£596.38, 10%	TA366 2015
	Outpatient cost, %	£156.84, 90%	TA366 2015
	Mean cost per patient	£200.79	TA366 2015
Hypertension		£287.04	EB04Z: outpatient procedure
Hyponatraemia	Cost assumed £0	Cost assumed £0	TA366 2015
Keratoacanthoma		£198.66	JC41Z: outpatient major skin procedure
Pain in extremity	Outpatient cost	£139.52	HRG service code 191, pain management
Rash		£137.31	TA269 2012
Rash-maculo popular		£137.31	TA269 2012
Squamous cell carcinoma of skin		£198.66	JC41Z: outpatient major skin procedure

* Alanine aminotransferase increase, aspartate aminotransferase increase, gamma-glutamyltransferase increase, blood alkaline phosphatase increase, blood creatine phosphokinase increase

AE costs were then estimated as the total weekly AE cost per patient using incidence data from the coBRIM trial and unit cost estimates from previous STAs and HRG unit costs. These costs were estimated to be £3.20 for vemurafenib + cobimetinib and £3.90 for vemurafenib. For dabrafenib, safety data were not available at the same level of detail so that AE cost were assumed to be the same as the lower vemurafenib + cobimetinib cost. However, the CS states that the difference in AE costs between intervention and vemurafenib was mainly due to the

higher incidence of squamous cell carcinoma in the vemurafenib group. This was also one of the very few AEs for which the difference in incidence between vemurafenib + cobimetinib and vemurafenib was statistically significant. The ERG therefore concludes that the use of differential AE cost between intervention and vemurafenib appears to be justified for the base case analysis. However, the same AE cost for all therapies should be tested within scenario analysis. The ERG tested the effect of using the same AE for all therapies and found that the model ICERs were not significantly affected by this change.

4.3.7.5 Other costs assumed in the model

Apart from the costs summarised above, the only additional cost considered in the economic model was for BRAF mutation testing. However, as this is part of routine management for patients with advanced melanoma in the UK, the diagnostic cost at a rate of £95 was applied to both the intervention and comparators and does not impact on the incremental cost in the model.

Further, the company assumed that post-progression would be the same for the intervention and comparators so no costs were included for active treatment after progression.

4.3.7.6 Bottom-line summary of ERG view on resource use

Resource use considered in the economic model consists of drug cost, dispensing cost, treatment of AEs, weekly supportive care (health state cost), and diagnostic cost. Resource use has been estimated either directly from the coBRIM trial, the published literature or previous STAs on advanced melanoma in the UK. Unit costs for resources were obtained from previous STAs and HRG reference costs. The cost year varies by resource item between 2009 and 2014/15. In general, the approach to estimate resource use and cost appears to be justified and reasonable.

However, the ERG has a few concerns over the costing methodology to estimate drug cost, time on treatment, health state cost, and the cost of AEs. First, drug cost should be estimated using either label doses throughout all treatment options or by reflecting dose modification for all drugs. Further to that, the ERG suggests scenario analysis with decreasing health state cost for long term stable PD as there is evidence suggesting that healthcare cost decrease in these patients. Finally, a scenario should be tested which assumes identical AE costs between

intervention and both comparators, as only very few differences in the incidence of AEs between treatment arms were observed in the coBRIM trial.

4.3.8 Cost effectiveness results

Deterministic results from the economic model are presented (CS Section 5.7, page 138) as incremental cost per QALY gained for vemurafenib + cobimetinib compared with vemurafenib and with dabrafenib. Results are also reported for total life years. Base case results are shown for the drug list price of the treatment with further results presented in CS Appendix 14 with PAS discounts included for vemurafenib and dabrafenib.

For the base case, an incremental cost per QALY gained of £150,514 is reported (see Table 22) for vemurafenib + cobimetinib compared to vemurafenib and £209,942 for vemurafenib + cobimetinib compared to dabrafenib. As these analyses have been conducted using different assumptions, the company has not provided an analysis that compares all three treatments with each other incrementally. It is not possible to combine the two analyses in one incremental analysis because the analyses have used different assumptions.

Table 22 Deterministic base-case results, (list prices), for direct treatment comparison (actual TOT used) (CS Table 46)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/ (QALY gained)
Vemurafenib + cobimetinib	£163,974	3.034			
Vemurafenib	£81,984	2.489	£81,990	0.545	£150,514

Table 23 Deterministic base-case results, (list prices) for indirect treatment comparison (PFS as surrogate for TOT) (CS Table 47)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/ (QALY)
Vemurafenib + cobimetinib	£208,047	3.034			
Dabrafenib	£78,392	2.417	£129,655	0.618	£209,942

4.3.9 Assessment of uncertainty

The company conducted a range of sensitivity analyses including deterministic sensitivity analyses and PSA.

4.3.9.1 Probabilistic sensitivity analysis

The company performed PSA with the distributions used for the input parameters shown in CS Table 44. The company used the gamma distribution for the utilities, the multivariate normal distribution for the parametric survival curves and log normal distribution for the costs. The ERG considers a more standard approach is to use the beta distribution for the utilities. The ERG re-ran the PSA using 1000 simulations which took approximately 2.5 minutes. We note that the utilities for PFS and progressed disease have been varied independently. However, it would be more correct if these utilities were correlated for each health state. The PSA results are relatively consistent with 1000 iterations and we consider this number of iterations is sufficient.

The PSA results are shown in CS Tables 57 and 58 (Table 24 and Table 25 of this report) and give similar results to the deterministic base case results. The CS summarises the results of the PSA stating that there is a 0% probability of vemurafenib + cobimetinib being cost-effective, relative to vemurafenib at a threshold willingness to pay of £50,000 per QALY gained. Furthermore, the CS stated that for all simulations the cost of vemurafenib + cobimetinib treatment was higher than vemurafenib treatment and the total QALYs was higher for patients treated with vemurafenib + cobimetinib than those treated with vemurafenib. A scatterplot of the PSA results is given in CS Figure 32 (Figure 11 of this report).

Table 24 Mean results of PSA compared to base case (list prices) for vemurafenib + cobimetinib vs. vemurafenib (CS Table 57)

	Costs	QALYs	ICER
Vemurafenib + cobimetinib	£164,636	3.028	£151,668
Vemurafenib	£81,615	2.480	

Table 25 Mean results of PSA compared to base case (list prices) for vemurafenib + cobimetinib vs. dabrafenib (CS Table 58)

	Costs	QALYs	ICER
Vemurafenib + cobimetinib	£210,076	3.028	£215,264
Dabrafenib	£79,472	2.421	

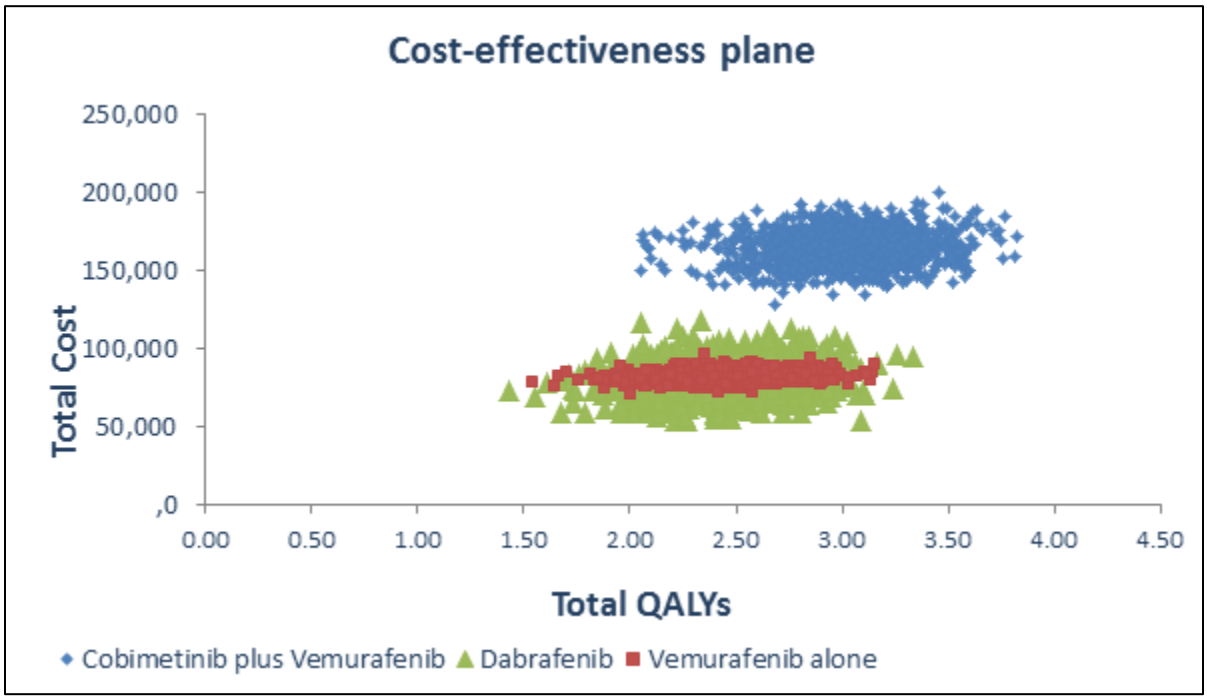


Figure 11 Scatterplot of PSA results for cost effectiveness plane (CS Figure 32)

4.3.9.2 Deterministic sensitivity analyses

The CS provides deterministic sensitivity analyses for six input parameters that are stated to have the greatest impact on percentage increment in costs or QALYs. These are shown in CS Table 59 and shown in this report in Table 26. The CS does not comment on the ranges used for the sensitivity analyses. The ranges were based upon the 95% CIs for the PFS utility state, but arbitrary ranges appear to be chosen for the cost input parameters and utility for PD. The ERG found that there was an error in the calculation of the sensitivity analysis for the weekly cost of vemurafenib, as the cost for vemurafenib was only altered in the vemurafenib + cobimetinib arm and not altered in the vemurafenib only arm. The ERG's corrected values for this parameter varied between £126,111 and £174,916. The parameters that have the largest impact on the model results are for the utility for PFS and the cost of cobimetinib. However, the sensitivity analyses for PFS utility should be treated with caution, as the PFS utilities of the two treatment arms have been varied independently, whereas the ERG considers they would be highly correlated. The company has not included sensitivity analyses for the effectiveness of the treatment or the cure rate. The ERG conduct these sensitivity analyses in Section 4.4

Table 26 Deterministic sensitivity analyses (CS Table 59) (List prices)

Variable	Range (% of base case)	Resulting ICER using lower value	Resulting ICER using higher value
Weekly cost cobimetinib	±50%	£101,933	£199,082
Weekly cost vemurafenib	±50%	£60,248[a]	£240,568[a]
Supportive costs (PFS)	±50%	£144,209	£156,820
Utility PFS vemurafenib + cobimetinib	25th percentile: 0.736; 1	£209,002	£103,686
Utility PFS vemurafenib	25th percentile 0.735;1	£131,025	£221,505
Utility PD	0.5; 1	£176,090	£90,579

[a] The ERG's calculated ICERs for weekly cost of vemurafenib is £126,111; £174,916

4.3.9.3 Scenario analysis

The company conducted scenario analyses to assess the uncertainty around structural assumptions of the model. Results are shown in CS Table 60 (and Table 27 of this report) for the following scenarios: alternative OS and PFS parametric distributions; utility values; dose / treatment duration assumptions; discount rate; time horizon; zero drug cost for cobimetinib.

The CS states that without PAS discounts there are no conditions at which the ICER is below the acceptable threshold. The results show that at zero cost for cobimetinib, the ICER for vemurafenib + cobimetinib compared to vemurafenib is £53,358 per QALY. Vemurafenib + cobimetinib is not cost effective at zero price because patients are treated until disease progression and so the treatment costs are increased because of longer PFS in the vemurafenib + cobimetinib arm compared to the vemurafenib + placebo arm.

The model results were most sensitive to changes in the parametric distributions used for OS and the assumption used for TOT. The ERG has conducted additional scenario analyses for the case where there is no cure rate fraction incorporated and changing the TOT extrapolation curve for vemurafenib + cobimetinib to KM with a log-logistic tail in Section 4.4.

Table 27 Scenario analysis results for vemurafenib + cobimetinib vs vemurafenib or dabrafenib (List prices)

Scenario	Base case	Analyses	ICER intervention vs. vemurafenib	ICER intervention vs. dabrafenib
Base case	n/a	n/a	£150,514	£209,942
	OS parametric distribution			
1	Lognormal	Exponential	£161,902	£219,912
2		Weibull	£229,890	£269,146
3		Log-logistic	£175,592	£212,255
4		Gompertz	£253,766	£269,898
5		Gamma	£217,135	£262,084
	PFS parametric distribution			
6	Log-logistic	Exponential	£166,292	£193,165
7		Weibull	£157,072	£169,530
8		Gamma	£164,485	£191,655
9		Lognormal	£157,377	£203,455
10		Gompertz	£152,215	£164,942
	Utilities			
11		Alternative health state utilities using the OHE value set for EQ-5D-5L valuation	£143,536	£200,778
12		Alternative health states utilities using one value (0.59) for all PD	£157,952	£219,640
	Dose / treatment duration			
13	Weibull	KM with Exponential tail for vemurafenib + cobimetinib (when in combination), TOT	£137,839	£209,942
14	Log-logistic	KM with Lognormal tail for vemurafenib (when monotherapy), TOT	£159,817	£209,942
15		PFS as a proxy for TOT for vemurafenib + cobimetinib vs. vemurafenib	£221,732	£209,942
16		Dosing as per label for vemurafenib + cobimetinib vs. vemurafenib	£170,305	£254,301
	Discount rate: effects and costs			
17	3.5%	1.5%	£140,198	£203,763
	Time horizon			
18	30	20	£152,911	£209,811
19		10	£169,632	£217,655
	Drug costs			

20		£0 cobimetinib	£53,358	£90,977

4.3.10 Model validation

Internal consistency

The company reported (CS page 155) that clinical and health economic experts were consulted in the construction of the economic model to validate the methodological and clinical assumptions and to verify that the model outputs were clinically plausible. Aspects discussed with experts included: the model structure and health state; the mix model for OS extrapolation; derivation of the utilities from the coBRIM trial; resource use within the model.

The company reported that internal consistency of the model had been conducted by York Health Economics Consortium (YHEC) and consisted of a number of tests, including using extreme values.

The economic model is coded in Microsoft Excel and is fully executable. The model is well presented and intuitive to use. The ERG has not undertaken a comprehensive check of all cells in the model, rather, internal consistency checks have been performed and random checking of the model has been done for some of the key equations in the model. The ERG have performed a detailed checking of all model inputs reported in the CS (white box testing); changing the parameter values produced intuitive results (black box testing) and from random checking the 'wiring' of the model appears to be accurate. The ERG was able to replicate the results presented in the CS and the deterministic sensitivity analyses, as reported in CS Tables 59 and Tables 60. The ERG views the model as a reasonable approach to modelling the cost effectiveness of advanced melanoma.

External consistency

The CS does not report a comparison of the results from the economic model with coBRIM trial. The ERG has compared the results from the economic model for PFS and OS and considers that the model provides comparable outcomes with those from the coBRIM trial.

The CS does not compare results from its analysis with analyses from other NICE technology appraisals for other BRAF inhibitors. The ERG compared the results for previous NICE

technology appraisals that reported the results for BRAF mutation positive patients treated with vemurafenib (Table 28). The results for the current appraisal are compared to the previous NICE appraisals TA319 of ipilimumab,[6] TA366 for pembrolizumab,[9] and TA384 for nivolumab.[4] The costs for patients treated with vemurafenib are similar between appraisals. The QALYs and life years vary between appraisals, with higher benefits in the CS compared with other appraisals. These variations are likely to be due to differences in assumptions used in the extrapolation of OS beyond the clinical trial data.

Table 28 Comparison of results patients treated with vemurafenib in the CS with previous NICE technology appraisals (list price)

Results for vemurafenib	Costs	QALYs	Life years
Current company submission	£81,984	2.49	3.39
TA319 ipilimumab	£80,658	2.13	2.98
TA384 nivolumab	Not available	1.69	2.37
TA366 pembrolizumab	£83,384	1.73	2.74

Results are not available for TA269 vemurafenib; TA321 dabrafenib

4.4 Additional work undertaken by the ERG

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the CS cost effectiveness analyses. This consists of additional sensitivity analyses for parameters that have not been adequately explored by the company and scenario analyses with alternative assumptions.

4.4.1 Sensitivity analyses

The ERG has completed the following sensitivity analyses:

i) Cure rate fraction

ii) Treatment effectiveness vemurafenib + cobimetinib vs vemurafenib (PFS, OS)

iii) Treatment effectiveness vemurafenib + cobimetinib vs dabrafenib (PFS, OS)

For each analysis, the ERG varied the parameter between its upper and lower 95% CIs/CrIs and the results are shown in Table 29.

Table 29 ERG deterministic analyses using 95% CIs/CrIs (using list prices)

Comparator / Scenario	Parameter value			ICER (£/QALY)	
	Base case	Low 95% CI/CrI	High 95% CI/CrI	Low 95% CI/CrI	High 95% CI/CrI
Vemurafenib					
Cure rate fraction	[redacted]	[redacted]	[redacted]	£149,166	£151,770
Vemurafenib PFS[a]	0.58	0.46	0.72	£161,467	£158,733
Vemurafenib OS[a]	0.70	0.55	0.90	£114,084	£310,905
Dabrafenib					
Dabrafenib PFS[b]	0.599	0.46	0.77	£219,956	£195,405
Dabrafenib OS[b]	0.635	0.47	0.86	£155,149	£404,450

[a] HR from coBRIM trial; [b] 1/AFT from NMA

Of these analyses, the sensitivity analyses for OS have most effect on the model results: changing the effectiveness of vemurafenib led to an ICER of between £114,084 and £310,905 per QALY gained.

4.4.2 Scenario analyses

The ERG conducted the following scenario analyses:

i) Cure rate fraction removed
ii) TOT extrapolation curve changed to KM with log-logistic tail
iii) Changes to utility values
iv) Consistency in dosing between vemurafenib + cobimetinib and dabrafenib
v) Shorter treatment duration
vi) Inclusion of subsequent treatment costs
vii) Assuming equal efficacy between vemurafenib and dabrafenib for OS
viii) Combination analysis of scenarios ii), iii) and iv)

The results of the scenario analyses are shown in Table 30 and discussed below.

Table 30 ERG scenario analyses (using list prices)

Comparator / Scenario	Base case	Value used in analysis	vs. vemurafenib ICER (£/QALY)	vs. dabrafenib ICER (£/QALY)
Base case results:	-	-	£150,514	£209,942
i) Cure rate fraction	[redacted]	0	£137,928	£190,964

ii) TOT for vemurafenib + cobimetinib	KM with Weibull tail	KM with log-logistic tail	£204,340	£209,942
iii) Utility values PFS vemurafenib + cobimetinib	0.837	0.819	£158,414	£219,603
iii) Utility values PD	0.59; 0.77	0.73	£154,717	£211,447
iv) Dabrafenib dose	£1400 per week	£1232 per week	£150,514	£223,277
v) Shorter treatment duration	Treat until disease progression	Treat for a maximum 2 years	£123,478	£139,532
vi) Subsequent treatment	No subsequent treatment	Subsequent treatment £1400 / week	£149,669	£219,201
vii) Dabrafenib OS	0.635	0.7	£150,514	£243,836
viii) Combination analysis (scenarios ii,iii & iv)[a]	See scenarios above	See scenarios above	£210,046	£224,877

[a] The combination analysis includes changes for scenario iii only for PD utilities and not for PFS utilities.

i) Cure rate fraction removed

The company modelled OS by assuming a proportion of patients will have a low risk of cancer mortality represented by a cure rate fraction. For illustration this scenario explores the effect of removing the cure rate fraction, so that all patients are at a the same high risk of cancer mortality. This results in a reduction in the ICER to £137,928 per QALY gained for vemurafenib + cobimetinib compared to vemurafenib and a reduction in the ICER to £190,964 compared to dabrafenib.

ii) TOT extrapolation curve changed to KM with log-logistic tail

The ERG considers that the TOT should be modelled for both treatment arms with KM data with a log-logistic tail to allow consistency between treatment arms, rather than the company's approach which uses KM data with a Weibull tail for the intervention arm (as discussed in Section 4.3.5.3). Changing the TOT extrapolation results in an increased ICER of £204,340 per QALY for vemurafenib + cobimetinib compared to vemurafenib. The ICER compared with dabrafenib is unchanged because this analysis using a different method to estimate TOT.

iii) Changes to utility values

The ERG considered alternative utility values for the PFS and PD state. We changed the utility value for the PFS health state to be the same in both arms (0.819) and changed the utility value for the PD health state to 0.73 (as used in the NICE appraisal of nivolumab, TA384[4]), (as discussed in more detail in Section 4.3.6). The model results were not sensitive to changes in these utility values, with the ICER increasing to £158,414 per QALY gained compared to vemurafenib when changing the PFS utility value and £154,717 per QALY compared to vemurafenib when changing the PD utility value. Similar reductions in the ICER were seen in the comparison with dabrafenib.

iv) Consistency in dosing between vemurafenib + cobimetinib and dabrafenib

The ERG noted that in the comparison between vemurafenib + cobimetinib and dabrafenib, the company used the mean dose for vemurafenib + cobimetinib given in the coBRIM trial and the planned (label) dose for dabrafenib (which was not included in the trial). However, the mean dose of vemurafenib + cobimetinib was lower than the planned dose in the trial. For consistency, we used the same reduction in dosage for dabrafenib as seen in the trial for vemurafenib + cobimetinib (12%). This resulted in an increased ICER of £223,277 per QALY gained.

v) Shorter treatment duration

The ERG conducted an illustrative scenario whereby patients could be treated for a shorter duration, contrary to the current marketing authorisation of treating until disease progression. For simplicity, we conservatively assumed that there would be no loss in treatment effect due to the shorter treatment duration. Under the hypothetical assumption of maximum treatment duration of two years, the ICER reduced to £123,478 per QALY for vemurafenib + cobimetinib compared to vemurafenib and reduced to £139,532 compared to dabrafenib. However, we advise caution on the interpretation of this scenario as it is unclear what effect shorter treatment duration would have on health outcomes. Furthermore, expert clinical advice to the ERG was that in clinical practice responding patients would be unlikely to stop treatment before disease progression if they have acceptable toxicity.

vi) Inclusion of subsequent treatment costs

The CS did not include subsequent anti-cancer drug treatment in the economic model. The ERG considered an illustrative scenario whereby all patients received subsequent anti-cancer treatment when their disease progressed. This was assumed to be at the same price as dabrafenib, i.e. £1400 per week for as long as patients remained alive. This illustrative scenario showed that including subsequent anti-cancer drug treatment in the economic model would have had a minimal impact on model results.

vii) Assuming equal efficacy between vemurafenib and dabrafenib for OS

As discussed in Section 3.1.7.4 of this report, patient crossover from dacarbazine to dabrafenib occurred in the BREAK-3 trial and the effect of this does not appear to have been taken into account in the company's NMA. We consider that this would underestimate the clinical effectiveness of dabrafenib. We are not able to perform the necessary adjustment and therefore provide an exploratory analysis that assumes similar effectiveness for dabrafenib as for vemurafenib, as accepted in the previous NICE technology appraisal of dabrafenib.[7] Using the same OS estimates for dabrafenib and vemurafenib increases the ICER for vemurafenib + cobimetinib compared dabrafenib to £243,836 per QALY.

viii) Combination analysis of scenarios ii), iii) and iv)

The scenario combines ERG scenarios ii), iii) and iv), i.e. changes to the TOT for vemurafenib + cobimetinib; changes in utility values for the PD state (NB. there are no changes to the utility values for the PFS health state); and alterations to the dosing schedule for dabrafenib. The combination scenario provides the basis for the ERG's base case, discussed in the following section. The scenario increases the ICERs for vemurafenib + cobimetinib compared vemurafenib to £210,046 per QALY and increases the ICER compared to dabrafenib to £224,877 per QALY.

4.4.3 SHTAC base case

Based upon our critique of the company's economic model, the ERG suggests an alternative base case (Table 31). Our base case analysis was conducted using a replication of the

company model based on the NMA for the comparison with vemurafenib + cobimetinib and vemurafenib and with dabrafenib (the company's model is informed by the coBRIM trial for the comparison with vemurafenib, and the NMA for the comparison with dabrafenib).

Table 31 Base case specification

	Company base case	**SHTAC base case**
Analysis	Pairwise comparison for vemurafenib + cobimetinib vs vemurafenib; vemurafenib + cobimetinib vs dabrafenib.	Fully incremental analysis comparing vemurafenib + cobimetinib, vemurafenib and dabrafenib.
PFS	Loglogistic distribution fitted to coBRIM trial data for direct comparison. The indirect treatment comparison used the parametric distribution for vemurafenib + cobimetinib adjusted using the AFT.	The same approach was used as in the company base case. In the incremental analysis, PFS estimates for vemurafenib were derived from the NMA rather than the coBRIM trial. This was done for methodological consistency to enable a fully incremental analysis to be conducted.
OS	[redacted] distribution fitted to the coBRIM trial data for direct comparison. The indirect treatment comparison used the parametric distribution for vemurafenib + cobimetinib adjusted using the AFT.	The same approach was used as in the company base case. In the incremental analysis, OS estimates for vemurafenib were derived from the NMA rather than the coBRIM trial. This was done for methodological consistency to enable a fully incremental analysis to be conducted.
Time on treatment (TOT)	Time on treatment estimated with fitted parametric curves to KM data for time on treatment for direct comparison. KM data used with parametric extrapolation ('tail') with Weibull for vemurafenib + cobimetinib and loglogistic for vemurafenib. For indirect comparison, the PFS curve was used a proxy for time on treatment.	In the incremental analysis, TOT was estimated using the NMA. The PFS curve was used as a proxy for time on treatment. (ERG scenario ii) In the incremental analysis the drug costs were reduced by 7% to allow for the differences between actual TOT and time on treatment predicted using PFS.
Costs	Health state costs based upon MELODY study. Adverse event costs included based upon those in the coBRIM trial.	We used the same costs as the company except for the dabrafenib costs which were reduced by 12% for consistency with the drug dosages used in the coBRIM trial (ERG scenario iv).
Utilities	HRQoL taken from coBRIM trial	HRQoL taken from the coBRIM trial for

	for PFS and from Beusterien et al. for progressed disease.	PFS and from nivolumab NICE TA384 for progressed disease. (ERG scenario iii).
Time horizon	Lifetime	Lifetime
Discounting	3.5% per year for cost and effects	3.5% per year for cost and effects

The company did not provide a fully incremental analysis comparing vemurafenib + cobimetinib to both vemurafenib and dabrafenib monotherapies. Rather, two separate pairwise comparisons were provided. These analyses are not easily combined to form an incremental analysis as different assumptions have been used, i.e. differences in the methods used to extrapolate survival and to estimate time on treatment. The ERG conducted a fully incremental analysis by using comparative effect estimates for vemurafenib and for dabrafenib from the NMA (notwithstanding our caveats about the validity of the NMA, see Section 3.1.7), along with the assumptions from the SHTAC preferred base case. We used the same assumptions for extrapolation of survival and estimation of time on treatment for the comparisons with vemurafenib and dabrafenib.

Our preferred base case includes changes to the extrapolation of TOT (scenario ii), changes to the utility values for PD (scenario iii) and a consistent dose estimation for vemurafenib + cobimetinib and for dabrafenib (scenario iv). The extrapolation of TOT using the KM with log-logistic tail allows a consistent approach for extrapolation between study arms. Similarly there was an inconsistency in the approach in the company's model for the treatment dosage between vemurafenib + cobimetinib and dabrafenib and we have used consistent dose estimation for both treatment arms.

In addition to the changes for scenario ii, iii and iv (combination scenario viii), another adjustment was made for the vemurafenib and dabrafenib analyses. The company's base case indirect treatment comparison uses drug costs, drug administration and AE costs based on PFS as a proxy which overestimates these costs compared to those observed in the trial analysis by about 7%. These costs have been multiplied by 0.93 to give them a better approximation.

The analysis is shown in Table 32 using the drug list prices and in a separate confidential appendix for the NICE Appraisal Committee with the PAS discounted prices.

Table 32 ERG analysis: Fully incremental analysis (using list prices)

	QALY	Cost	Incremental QALY	Incremental Cost	ICER (£/QALY)
Dabrafenib	2.479	£65,908			
Vemurafenib	2.576	£77,846	0.10	£11,938	£123,072
Vemurafenib + cobimetinib	3.092	£193,295	0.52	£115,449	£223,738

4.5 Overall summary of cost effectiveness

The structure of the economic model was appropriate, comprehensive and reflected the clinical pathway for patients with advanced melanoma. The economic model, developed in Microsoft Excel, was well structured and intuitive. The ERG did not find any errors in the coding of the model structure.

The methods chosen for the analysis were generally appropriate and conformed to NICE methodological guidelines. However the treatments were not compared in a fully incremental analysis, due to differing methods used for the comparison of vemurafenib + cobimetinib with vemurafenib and dabrafenib.

The CS base case analyses for vemurafenib + cobimetinib compared to vemurafenib had an ICER of greater than £150,000 per QALY (using list prices) and the CS stated that vemurafenib + cobimetinib would not be cost effective at a threshold of £50,000 per QALY even if the price of cobimetinib was reduced to zero. Vemurafenib + cobimetinib is not cost effective at zero price because patients are treated until disease progression and so the treatment costs are increased because of longer PFS in the vemurafenib + cobimetinib arm compared to the vemurafenib + placebo arm. To illustrate, the vemurafenib treatment cost for patients in the vemurafenib + cobimetinib arm is £98,285 compared to £71,699 in the vemurafenib monotherapy arm.

In general, the ERG considers that the choice of parameters used in the model and choice of parametric curves used for extrapolating beyond trials data were reasonable. However we identified several areas where we suggest alternative data sources or parametric curves would be more appropriate. Given the uncertainty over extrapolating beyond clinical trial data, other parametric curves may also be plausible and in all cases these would result in a less favourable ICER. The ERG had reservations about the parametric curve used to fit time on treatment for

vemurafenib + cobimetinib. The ERG suggests using the KM data followed by a log-logistic tail would be consistent with the curve used for PFS and the vemurafenib + placebo arm.

The ERG noted that in the comparison between vemurafenib + cobimetinib and dabrafenib, the company used the actual dose for vemurafenib + cobimetinib and the planned dose for dabrafenib. However the actual dose was lower than the planned dose in the trial. For consistency, the ERG suggests using the same reduction in dosage for dabrafenib as seen for vemurafenib in the coBRIM trial.

Based upon the ERG's analyses the preferred base case ICER for vemurafenib + cobimetinib compared to vemurafenib is likely to be at least £223,738 per QALY.

5 END OF LIFE

CS Section 4.13.2 (CS Table 26) provides the company's justification for why vemurafenib + cobimetinib combination therapy meets all of NICE's end of life criteria. Two of the three criteria relate to the condition under appraisal (melanoma) and have been accepted as meeting the end of life criteria in previous NICE appraisals of treatments for advanced (unresectable or metastatic) melanoma (e.g. NICE TA269[26]; NICE TA384[4]). That is, the treatment is indicated for patients with a short life expectancy, normally less than 24 months, and is licensed for small patient populations. In terms of the latter, the CS estimates that there would be 576 patients eligible for vemurafenib + cobimetinib treatment in England and Wales. This is based on the assumption that 34% of patients with malignant melanoma would have the mutated BRAF V600 gene, though other sources suggest that around 50% of cutaneous melanomas harbour the gene.[12] As stated earlier in this report, expert clinical advice to the ERG is that the majority of BRAF mutation positive patients would be considered for immunotherapy as first line treatment. All of these factors suggest that the estimate of 576 patients is uncertain.

The third criterion, that the treatment offers an extension to life normally of at least an additional three months, is reported to have been met by median OS from the coBRIM trial showing a statistically significant increase of nearly five months. As Table 10 of this report shows, the difference in median OS between combination therapy and vemurafenib monotherapy was 4.9 months and therefore in excess of NICE's threshold (NB. an equivalent difference between combination therapy and dabrafenib monotherapy is not reported in the submission, though the NMA did report a survival benefit in favour of combination therapy in this comparison). In

summary, the ERG agrees with the company's assertion that combination therapy meets the end of life criteria.

6 INNOVATION

The CS provides a rationale for why vemurafenib + cobimetinib should be considered an innovative therapy (CS Section 2.5). It describes how the addition of cobimetinib to vemurafenib offers inhibition of MEK which reduces the possibility of drug resistance to monotherapy. The clinical efficacy and safety results of the coBRIM trial appear to support this mechanism, and hence the rationale for combination therapy. The ERG notes that the benefits of this innovation will be more apparent in patients for whom BRAF inhibitor therapy is considered to be the most appropriate first line treatment for advanced disease.

Vemurafenib + cobimetinib are taken orally, and are therefore more convenient than other forms of administration. It is noted in the CS that the advantages that this brings to patients social and working lives is not captured in the QALY calculations. The ERG notes that dabrafenib is also taken orally, but that the currently available immunotherapies (ipilimumab, pembrolizumab, and nivolumab) are administered intravenously.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The rationale for combination therapy in BRAF mutation positive advanced melanoma patients, as stated in the CS, is to reduce the likelihood of resistance to BRAF inhibition monotherapy. The combination of vemurafenib and cobimetinib is reported to simultaneously target mutated BRAF V600 proteins and MEK proteins in melanoma cells, resulting in stronger inhibition of intracellular signaling, decreased tumour cell proliferation and thereby limit mechanisms of resistance to BRAF inhibition by vemurafenib monotherapy. The coBRIM trial found that median PFS was increased by between 3.7 and 5.3 months (depending on which analysis used) by vemurafenib + cobimetinib versus vemurafenib. Similarly, median OS was also increased by just under five months. Likewise, the company's NMA reported superior efficacy for vemurafenib + cobimetinib compared with dabrafenib in terms of PFS and OS, though the ERG has noted caveats about the validity of the indirect comparison. The results therefore provide some degree

of support the assertion that this combination therapy is more efficacious than BRAF inhibitor monotherapy, in terms of survival outcomes.

Combination therapy appears to be generally well tolerated, though in the coBRIM trial Grade 4 AEs appeared to be more common in the vemurafenib + cobimetinib group.

[redacted]

[redacted]There also appears to be a HRQoL advantage associated with combination therapy, with improvements resulting from less insomnia and/or other factors (e.g. the incidence of non-melanoma skin cancers). However, it is unclear whether these analyses would be statistically significant, and the durability of improvements over the treatment period and beyond is uncertain.

The coBRIM trial included centres in United States, Canada, Australia, New Zealand, Europe, Russia, Turkey, and Israel. There were a small number of patients from the UK and in terms of generalisability the CS suggests that the outcomes of the study were as would be expected in UK patients. Expert clinical advice to the ERG was that the patients in the coBRIM trial are similar to those seen in the UK. It is noted that the inclusion criteria excluded patients with poorer prognosis (e.g. patients with life expectancy <12 weeks were not eligible), but expert clinical advice to the ERG was that these patients would still be treated with targeted therapy. Further, as stated earlier in this report, the trial did not include patients who had previously been treated for advanced disease, even though the scope of this NICE appraisal permitted previously treated patients. As noted earlier, many BRAF mutation positive patients would be treated with immunotherapy first line before switching to BRAF inhibitor and MEK inhibitor treatment as necessary. The CS does not take this into account in its modelling of cost-effectiveness, though expert clinical advice to the ERG is that there are no data to suggest that outcomes would be worse for second line treatment.

7.2 Summary of cost effectiveness issues

The CS includes evidence on the cost effectiveness of cobimetinib in combination with vemurafenib compared to vemurafenib and dabrafenib for BRAF mutation positive patients with advanced melanoma. The economic evaluation generally conforms to the NICE reference case and the model structure and model parameter inputs are consistent with the clinical disease pathways and the available trial evidence. The CS used direct evidence from the coBRIM trial in

the comparison between vemurafenib + cobimetinib and vemurafenib and an indirect comparison using evidence from an NMA for the comparison between vemurafenib + cobimetinib and vemurafenib.

The company's base case analysis for vemurafenib + cobimetinib compared to vemurafenib was £150,514 per QALY gained using list prices. The company performed a wide range of sensitivity analyses, including deterministic, probabilistic and scenario analyses to assess model uncertainty. However in all analyses the cost effectiveness estimates were higher than £50,000 per QALY gained. Furthermore the company's PSA analyses showed a 0% probability that vemurafenib + cobimetinib would be cost effective at a willingness to pay of £50,000 per QALY. The ERG suggests an alternative approach for modelling time on treatment and this would further increase the ICER to £204,340 per QALY gained for vemurafenib + cobimetinib compared to vemurafenib. Additional sensitivity and scenario analyses conducted by the ERG resulted in ICERs above £100,000 per QALY gained for all analyses.

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Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma

Changes needed to the model to estimate the Southampton Health Technology Assessments Centre (SHTAC) base case incremental analysis

The SHTAC base case makes the following changes:

i) Changes to the TOT for vemurafenib + cobimetinib to KM + log-logistic tail;
ii) Changes to utility values for PD to 0.73;
iii) Changes to dabrafenib dose, reduce weekly cost by 12%;
iv) Adjustment to the cost of PFS drug costs, adverse event costs and drug administration costs to allow for difference between PFS proxy and TOT. Reduce by 7%. (see model inputs!g414)

In order to compare treatments in an incremental analysis, the NMA data estimates are used for vemurafenib and dabrafenib vs vemurafenib + cobimetinib.

For cobimetinib + vemurafenib the actual costs from the direct trial evidence are used (ie from Results Table).

For dabrafenib, this analysis is already completed in the indirect treatment comparison worksheet and so the steps i-iv) above are completed.

For vemurafenib, the indirect treatment comparison sheet is used for vemurafenib instead and dabrafenib, by changing the PFS/OS AFT factors in the 'ITC parameter sheet' and the drug cost to that for vemurafenib and then steps i-iv above are completed. Results are shown in Results Table (ITC) sheet.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

You are asked to check the ERG report from School of Health Related Research to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 27th April 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Correction of adverse event discontinuation rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11. Text from report: *'Fewer patients discontinued treatment due to AEs in the vemurafenib + cobimetinib group than vemurafenib + placebo group (42.1% vs 58.6%)'* Discontinuation rates due to adverse events (AEs) are incorrectly stated as 42.1% and 58.6% for vemuranfenib+ combimetinib and vemurafenib + placebo respectively.	Rates should read: *Overall, the rate of discontinuation due to AEs was higher in the cobimetinib plus vemurafenib arm compared with the placebo plus vemurafenib arm: cobimetinib or placebo (18.6% vs. 9.3%), vemurafenib (17.0% vs.9.3%), or both drugs (14.6% vs. 8.5%).* Ref: Page 40 coBRIM final CSR The discontinuation rates due to AEs taken from the most recent safety analysis (September 2015 data cut-off).	Rates incorrectly stated implying a higher discontinuation due to adverse events than was seen in the coBRIM study.	We agree that the statement as written is incorrect. However, if we amend using the wording as suggested by the company this would introduce inconsistency with the table in the main body of the ERG report (Table 15) which the statement is based on, as the company's suggested wording is from a more recent data cutoff (September 2015), than the cutoff in Table 15 (9th May 2014). For simplicity we have corrected the statement using the May 2014 data. [redacted]

Issue 2 Correction of data source for discontinuations due to non-compliance or physician decision

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11. Text from report: *'However, non-compliance was*	Rates should read: *However, non-compliance was higher when treated with cobimetinib (0.4% vs 0% placebo),*	Inconsistent use of study analysis data-cuts within same paragraph. Either primary analysis, or update analysis should be reported within	This is not a factual error as the data are all from the same data cutoff (9th May 2014). We think that the company may

higher when treated with cobimetinib (0.8% vs 0% placebo), as were physician decided discontinuations from treatment (1.2% vs 0.4% placebo).' Inconsistency of data cut being reported. Prior safety reporting within this paragraph refers to the most recent safety analysis (September 2015 data cut-off). Figures for non-compliance and physician discontinuation are taken from the primary CSR (May 2014 data cut-off)	*as were physician decided discontinuations from treatment (1.6% vs 1.2% placebo)* Ref: Table 5, page 41 coBRIM final CSR	paragraph.	have raised this in anticipation that we would have included data on discontinuation from AEs from the later cutoff of September 2015, as in issue 1 described above.

Issue 3 Formatting error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 Formatting error in second half of page. Paragraph beginning '*Certain drugs selectively target…'* repeated twice	Removal of repeating paragraph	Clarification of report	This was due to a formatting error in Microsoft Word. The paragraph has now been removed.

Issue 4 Incorrect description of nivolumab NICE guidance

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18 Incorrect description of nivolumab	As per TA384, title should read: *Advanced (unresectable or metastatic)*	Incorrect description of existing NICE guidance	Title amended

NICE guidance. Title reads: *Advanced melanoma not previously treated with ipilimumab (NICE TA 384)*	*melanoma (TA384)*		

Issue 5 Misinterpretation of systematic literature review inclusion criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 24, section 3.1.2 Section is in reference to study selection during systematic literature reviews, and discussion of inclusion and exclusion criteria used in systematic literature review. Reference is made to the inclusion criteria listed in table 6, page 38 of the CS. It is stated 'Life expectancy ≥12 weeks' is an inclusion criteria within this table. This statement is not an inclusion criteria for the systematic literature review, and is not found within table 6, page 38 of the CS. This is an inclusion criteria for the coBRIM study population, and is found in table 9, page 45 of the CS	Removal of the following wording from page 24 of the report: *…..although no reference can be found in the Summary of Product Characteristics (SmPC)11 in relation to the company's inclusions criteria of 'Life expectancy ≥12 weeks'. Expert clinical opinion to the ERG suggests that while the inclusion criteria were standard for a trial, in clinical practice patients with prognosis of <12 weeks life expectancy and a poor performance status will also be treated, as it is known that targeted therapy can salvage these patients.*	Incorrect interpretation of clinical study inclusions criteria as systematic literature review inclusion criteria.	Text amended

Issue 6 Reporting clinical advice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26 and 29 Text from report (page 26) *However, while these small imbalances might be expected to favour the placebo group, expert advice to the ERG did not consider that these differences would influence the improvement in clinical outcomes for those treated with cobimetinib.* Text from report (page 29): *It was stated that there were no statistically significantly differences between treatment groups (no p value reported) and expert clinical advice to the ERG suggests that these differences influence the improvements in clinical outcomes for those treated with cobimetinib.* Inconsistency on reporting of clinical advice to the ERG. Page 26 suggests study imbalances would not influence clinical outcomes, page 29 suggests study imbalance would influence clinical outcomes.	Correction of wording on page 29 to make consistent with wording on page 26. Suggested text to insert underlined below: *'It was stated that there were no statistically significantly differences between treatment groups (no p value reported) and expert clinical advice to the ERG suggests that these differences <u>would not</u> influence the improvements in clinical outcomes for those treated with cobimetinib.'*	Inconsistent reporting of clinical advice	Text amended

Issue 7 Citation error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29 Text from report: *While there were differences in patient's baseline characteristics between the treatment groups as previously stated (e.g. ECOG performance status, and metastatic status),*[10] Statement should be cited to reference 12 (Larkin J, Ascierto PA, Dréno B, et al. Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma. New England Journal of Medicine 2014;**371**(20):1867-76)	Suggested correction: *While there were differences in patient's baseline characteristics between the treatment groups as previously stated (e.g. ECOG performance status, and metastatic status),*[12]	Clarification of linked references	Citation number amended

Issue 8 Classification of adverse events collected in phase III study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 Incomplete definition of AE classification from coBRIM study	Suggested wording: *Adverse events (AEs) were classified as: all AEs, drug related AEs, deaths, SAEs, drug-related*	Accurate description of safety data collection and definitions within the coBRIM study	Not strictly a factual error, but the text has been amended as suggested.

Text in report: *'Adverse events (AEs) were classified as serious adverse events (SAEs), non-serious AEs of special interest (AESIs), and AEs leading to dose interruption or modification of treatment.'* Text in CS (page 32) *'The following safety parameters were summarised by treatment arm: all AEs, drug related AEs, deaths, SAEs, drug-related SAEs, AESIs, and AEs leading to dose interruption/modification and to discontinuation of study treatment.'*	*SAEs, AESIs, and AEs leading to dose interruption/modification and to discontinuation of study treatment.'*		

Issue 9 Definition of 1/AFT

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35: Text in report: *'(NB. the CS does not explicitly define if 1/AFT refers to the acceleration factor, or acceleration failure time)'* Page 83 of CS states: *'…..results of the NMA are presented as the inverse of the*	Removal of following text on page 35 *'(NB. the CS does not explicitly define if 1/AFT refers to the acceleration factor, or acceleration failure time)'*	Clarification of stated contents of CS	The point here is that the company doesn't define the acceleration factor - but implies it is the same as the accelerated failure time Text has been amended as suggested.

acceleration factor (1/AFT).'			

Issue 10 Completion rate of EQ5D in the phase III population in 'progressed disease' health state

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 55 Text in report: *'Although not stated in the clinical effectiveness section of the CS or in the company's clarification response, it is clear from the ERG's appraisal of the company's economic analysis that the EQ-5D was completed mostly by patients who had not progressed'* Page 114 of CS *Limited observations (n=57) are available for patients in the PD state.*	Removal of following text from report: *'Although not stated in the clinical effectiveness section of the CS or in the company's clarification response, it is clear from the ERG's appraisal of the company's economic analysis that….'* Text should read: *'The EQ-5D was completed mostly by patients who had not progressed'*	Clarification of stated contents of CS	Text amended

Issue 11 Incomplete citation of tables from clarification question responses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61: Footnote of table 14. Table is stated as being redrawn from Table 3 in the company's	Text should read: NB. This table has been redrawn from Table 2 and Table 3 in the company's clarification response to show AEs ordered according to	Clarification of data sources	Text amended

clarification response. Table 14 in ERG report is redrawn from tables 2 and 3 of the company's clarification response.	their difference between the trial arms		

Issue 12 Treatment duration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68: Text in report: *'Patients remain on treatment whilst they are in the PFS health state, as per the marketing authorisation for vemurafenib and cobimetinib.'* Clarification: Time on treatment is modelled according to the observed treatment duration in the coBRIM study. Treatment duration is taken from time on treatment curves rather than using PFS curves as a proxy.	Suggested text to insert underlined below: *Patients remain on treatment whilst they are in the PFS health state, as per the marketing authorisation for vemurafenib and cobimetinib. <u>Treatment duration is taken from time on treatment data from the coBRIM study, rather than from PFS results.</u>*	Clarification of data utilised for treatment duration	The ERG has added the suggested sentence to aid comprehension: '*Treatment duration is taken from the time on treatment data from the coBRIM study.'*

(please cut and paste further tables as necessary)