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

2nd Appraisal Committee meeting

19 July 2016

Issues for consideration

- With respect to adverse events, are there any advantages of vemurafenib over dabrafenib for committee to note?
- Is it reasonable for committee to assume clinical equivalence between vemurafenib and dabrafenib? Or should committee use the results from the NMA for the comparison of cobimetinib and vemurafenib versus dabrafenib with the accompanying assumptions used in the modelling?
- Is there any scenario in which cobimetinib in combination with vemurafenib can be considered cost effective?

ACD preliminary recommendation

1.1 Cobimetinib in combination with vemurafenib is not recommended within its marketing authorisation for treating unresectable or metastatic melanoma in adults with a BRAF V600 mutation.

Technology: cobimetinib in combination with vemurafenib

- 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
- 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. This may result in stronger inhibition of intracellular signalling, decreased tumour cell proliferation and may overcome resistance to BRAF inhibition by vemurafenib.

Drug administration

- Cobimetinib is taken orally on a 28 day cycle. It is taken for 21 days followed by a 7-day break
- Vemurafenib also given orally (days 1-28 of each cycle).
- For both, there is the possibility of down-dosing in response to toxicity and both drugs are continued until disease progression.
- Acquisition cost (excl. VAT) per 28 day cycle:
  - Cobimetinib tablets 63 x 20mg : £4275;
  - Vemurafenib tablets 224 x 240mg tablets: £4645
- No patient access scheme for cobimetinib is currently in place. An existing patient access scheme is in place for vemurafenib.

Clinical trial details

	CoBRIM
Population	Patients had BRAF V600 mutation-positive unresectable locally advanced (Stage IIIc) or metastatic melanoma (Stage IV), n=495
Intervention	Vemurafenib 960 mg twice daily days 1−28 Cobimetinib 60 mg once daily on days 1−21 of each cycle
Control	Vemurafenib 960 mg twice daily days 1−28 Placebo once daily on days 1−21 of each cycle (intervention and control continued until disease progression, unacceptable toxicity, or withdrawal of consent. No crossover)
Blinding	Double blinded
Patients and locations	No prior systemic therapy for advanced disease ECOG status: 0/1 135 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.

Source: Company submission: Figure 3 Study Design

Clinical trial results: progression free survival

Data cut-off	**May 2014** Median follow up 7.3 months (range 0.5-16.5 months). Pre-specified for primary outcome		**Jan 2015** Median follow up of 14.2 months	
	Cobimetanib + vemurafenib (n=247)	Vemurafenib + placebo (n=248)	Cobimetinib + vemurafenib (n=247)	Vemurafenib (n= 248) + placebo
PFS (months) Investigator assessed (95% CI) primary outcome	9.9 (9.0 to NR)	6.2 (5.6 to 7.4)	12.3	7.2
Hazard ratio	0.51, 95% CI 0.39 to 0.68		0.58, 95% CI, 0.46 to 0.728	

Source: Company submission table 16

Clinical trial results – overall survival

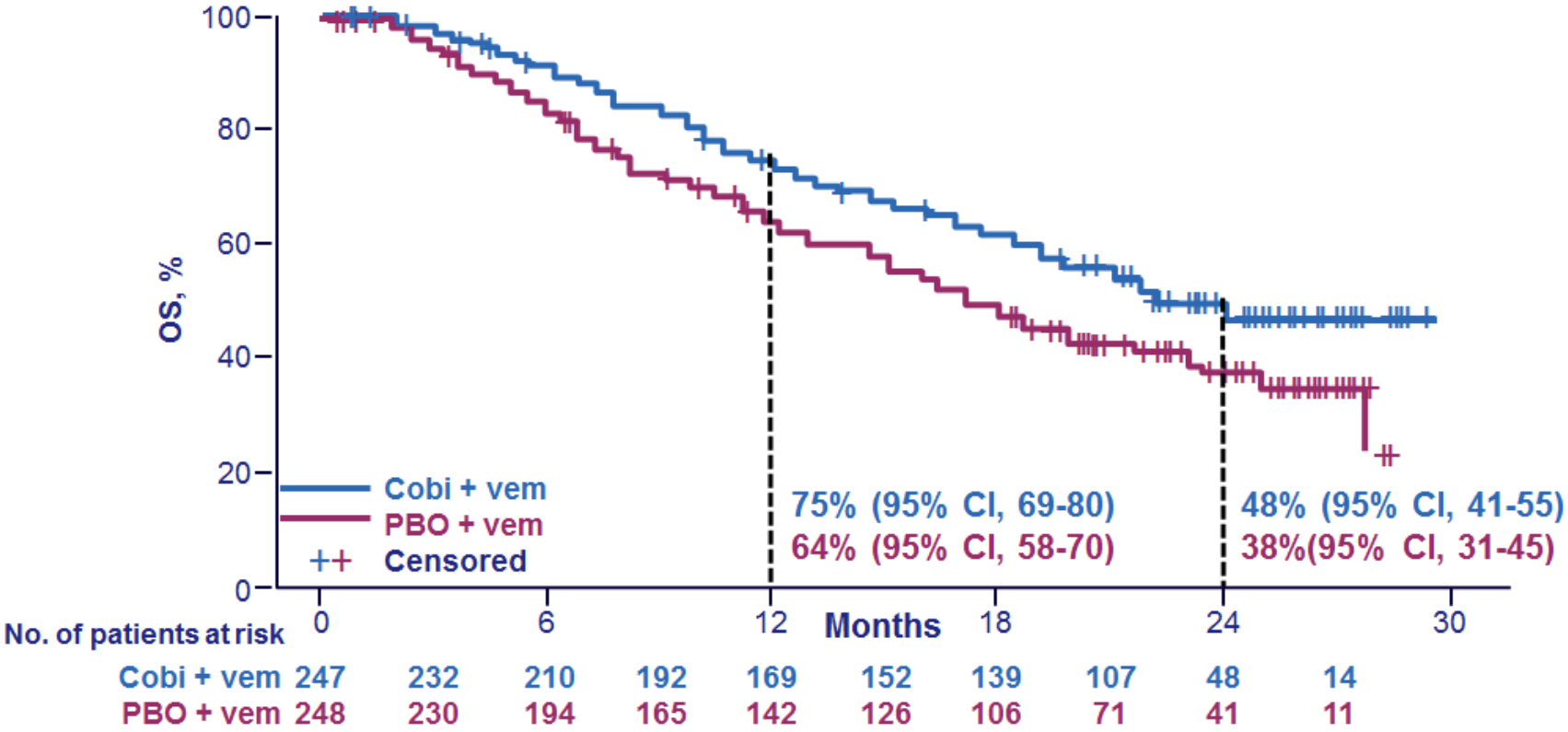
ERG critique: As only 255 events had occurred, the analysis of overall survival was likely to be underpowered to detect a difference between study arms

Data cut-off	**August 2015** Pre-specified for final overall survival analysis	
	Cobimetanib + vemurafenib (n=247)	Vemurafenib + placebo (n=248)
Median duration, months (95% CI)	22.3 (20.3 to not evaluable)	17.4 (15.0 to 19.8)
Hazard ratio for death	HR 0.70, 95% CI 0.55 to 0.90, p=0.005	

Source: Company submission tables 17

Overall survival

Kaplan Meier curve for overall survival in CoBRIM (ITT population)



Source: Company submission: Figure 7

Network meta-analysis
(no direct comparison with dabrafenib monotherapy)

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 (COMBI-v)	Trametinib 2mg + dabrafenib	Vemurafenib	

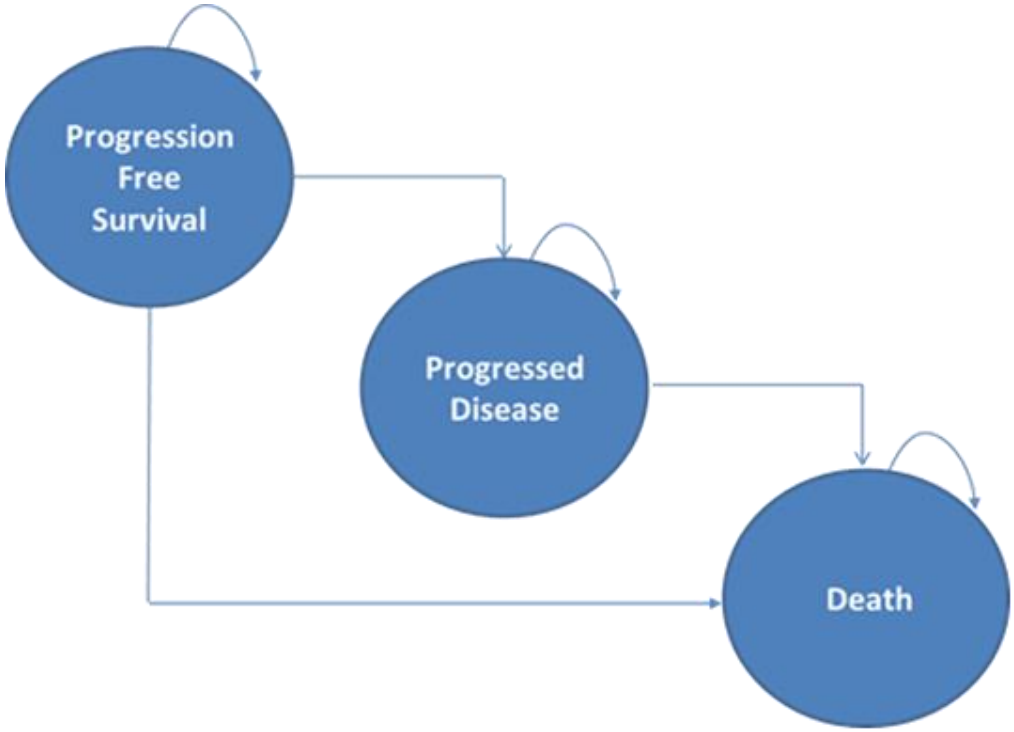
- Comparison cobimetinib + vemurafenib vs. dabrafenib (favours combination)
- Progression free survival 1/AFT 0.599, 95% CI 0.47 to 0.86
- Overall survival 1/AFT 0.635, 95% CI 0.46 to 0.77

Source: Company submission table 20 and page 86

ERG comments on network meta-analysis

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. 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. (note: no crossover in CoBRIM)

Model Structure



Time horizon: 30 years, cycle length 1 week with half cycle correction
Clinical data from CoBRIM (cobimetinib + vemurafenib vs. vemurafenib) and indirect treatment comparison (dabrafenib)

Health State Utility Values

	Treatment	Crosswalk	OHE algorithm	Beusterien *et al* (2006) TA267
Progression free survival (PFS)	Cobimetinib + vemurafenib	0.837 (0.004)	0.898	
	Vemurafenib (dabrafenib assumed same)	0.819 (0.004)	0.887	
Progressed disease (PD)	Cobimetinib + vemurafenib	0.798	0.862	
	Vemurafenib	0.801	0.865	
PD <5 yrs	All			0.590 (0.02)
PD ≥5 yrs	All			0.770 (0.02)

- EQ-5D 5L data collected in coBRIM: 2 methods for EQ-5D 5L to utility;
  - OHE values considered implausible so Crosswalk method data used for PFS state
- Beusterien data preferred for PD state, as it accounted for longer-term improvement in QoL

Resources and costs

- List prices of cobimetinib, vemurafenib and dabrafenib in base case
- Monthly costs of cobimetinib and vemurafenib adjusted based on dose modifications in coBRIM
- At request of NICE ERG produced confidential appendix showing results incorporating confidential patient access schemes for vemurafenib and dabrafenib

Time on Treatment

- 2 approaches used for time on treatment
  - cobimetinib + vemurafenib v vemurafenib: extrapolated from coBRIM
    - cobimetinib and vemurafenib using Weibull
    - vemurafenib using log-logistic
  - cobimetinib + vemurafenib v dabrafenib:
    - Progression free survival used as proxy (no time on treatment data)

Company's base case results*

	Total costs	Total LYG	Total QALYs	Inc £	Inc QALY (inc LYG)	ICER
Cobimetinib + vemurafenib	£163,974	4.015	3.034			
Vemurafenib	£81,984	3.392	2.489	£81,990	0.545 (0.622)	£150,514
Cobimetinib + vemurafenib	£208,047	4.015	3.034			
Dabrafenib	£78,392	3.281	2.417	£129,655	0.618 (0.733)	£209,942

* Deterministic pairwise comparisons using the list price for vemurafenib and dabrafenib. NB vemurafenib and dabrafenib are available to the NHS at a discounted price as agreed in the patient access schemes for TA269 and TA321 respectively

Source: Company submission, tables 46 and 47 page 147

Company's sensitivity analyses*

Additional sensitivity analyses included

- Assumptions on parametric distributions for PFS and OS
- Dose and treatment durations
- Utility values
- Discount rate and time horizon

- In all scenarios, the ICER remained above £130,000/QALY
  When the price of cobimetinib was set to £0, the ICER >£53K (combined with vemurafenib at list price)
  - Company: as no price could be considered cost effective by NICE methods, no Patient Access Scheme has been proposed

*using list prices for vemurafenib and dabrafenib

ERG base case results*

	Total QALY	Total costs	Inc QALY	Inc costs	ICER fully incremental	ICER pairwise cobimetinib + vemurafenib vs. comparator
Dabrafenib	2.479	£65,908				£207,809
Vemurafenib	2.576	£77,846	0.10	£11,938	£123,072	£223,738
Cobimetinib + vemurafenib	3.092	£193,295	0.52	£115,449	£223,738	

Key differences in results versus vemurafenib:
Costs – ERG **+£29k for C+V arm**; -£4k V arm
QALYs – ERG -+0.058 QALY for C+V arm; +0.087 QALY for V arm
Key differences in results versus dabrafenib
Costs – ERG **-15k for C+V arm**; -£12.5k D arm
QALYs – ERG + 0.058 QALY for C+V arm; +0.062 QALY for V arm

NICE

*using the list price for vemurafenib and dabrafenib ERG presented fully incremental results in its base case; NICE calculated pairwise ICERs

Committee conclusions ACD (1)

- Data from the CoBrim trial showed cobimetinib plus vemurafenib is clinically effective compared with vemurafenib alone.
- There were no head-to-head data comparing cobimetinib plus vemurafenib with dabrafenib and the company's indirect comparison was based on a network of a small number of trials and potential differences between the trials had not been fully accounted for.
  - the potential heterogeneity of the trials in the network had not been fully explored in the company's submission
  - BREAK-3 and BRIM-3 trials allowed crossover which was not accounted for in the NMA

Committee conclusions ACD (2)

- Given the uncertainty surrounding the indirect comparison, committee agreed the most important comparison was the clinical and cost effectiveness of cobimetinib plus vemurafenib compared with a monotherapy BRAF inhibitor, and that vemurafenib and dabrafenib may be interchangeable in this regard.
  - committee was inclined towards this approach because it had heard that vemurafenib and dabrafenib monotherapies are considered to be of similar clinical effectiveness
- Data from the coBRIM trial (comparing cobimetinib plus vemurafenib with vemurafenib) were considered to be the most robust clinical data available.
  - because there was less uncertainty surrounding the clinical trial results than the indirect comparison.

Committee conclusions ACD (3)

- The committee noted the comparisons with dabrafenib and vemurafenib used some different assumptions because of unavailability of some trial data for dabrafenib; they preferred the assumptions used for the vemurafenib comparison and thought that the clinical data used to inform these assumptions in the modelling was robust.
- There were limited trial data available on the quality of life in progressed disease, and the company and ERG presented different estimates for the utility of this state. The committee considered that a range of utility values should be considered in its decision making because it had heard from the clinical expert that quality of life may vary from person to person with advanced melanoma.

Committee conclusions ACD (4)

- Cobimetinib plus vemurafenib met end-of-life criteria and the committee took this into account in its decision making.
- In all of the analyses presented to the appraisal committee the incremental cost effectiveness ratios were over £100,000 per QALY gained. This is substantially over the range usually considered a cost effective use of NHS resources

Consultation comments

The following organisations responded:

- Company
- British Association of Dermatologists
- NHS England (no comment)

Company (1) – Approach to uncertainty of ITC for dabrafenib

- We consider it more robust to utilise results from the ITC, rather than the strong assumption of clinical interchangeability between two drugs for which no head to head data are available.
- The ERG considered the trials as broadly comparable, based on selected characteristics. For balance we believe the ACD should also make reference to this assessment by the ERG.
- Whilst we agree there is potential bias due to crossover, the consistency of results from the NMA vs. observed trial results, along with supporting scenario analyses using the ITC results from the random effects model, are supportive of the base-case results of the ITC.

Company (2) – adverse event profiles of comparators

- Section 4.3 of the ACD refers to discussion at the meeting regarding the adverse event profiles of the two comparators, vemurafenib and dabrafenib monotherapy.
- As we understood, the discussion was in reference to monotherapy BRAF inhibitor treatments being associated with different adverse event profiles. Within the ACD, only the adverse events more common with vemurafenib than dabrafenib are listed.
- To give a more balanced account, the adverse events more common with dabrafenib than vemurafenib should also be listed.

Company (3)

- When considering the list price for vemurafenib, at zero cost cobimetinib, 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. It is, therefore, factually accurate to state there is no cobimetinib price which could be cost-effective, when in combination with vemurafenib at list price.
- We acknowledge at zero cost cobimetinib, the combination may be cost-effective when considering the existing PAS for vemurafenib, however this scenario is reliant on making a new product freely available.

Company (4)

- Whilst a positive price is possible, this scenario requires a very large discount on the price of cobimetinib. We do not believe that such scenarios are sustainable for manufacturers, and do not consider them to be supportive of expanding patient access to innovative technologies.
- As acknowledged in the DSU-TSD, it is the methodology underlying the current approach to HTA, in combination with the application of the recognised cost-effectiveness thresholds across all appraisals (i.e. whether a combination treatment or otherwise), which leads to such levels of discount being required.

British Association of Dermatologists

- With combination treatment, there are significantly less number of squamous cell carcinomas and keratoacanthomas (around 9% compared to about 20% with single agent BRAF) which have a cost implication as they require excision usually by a dermatologist.

Issues for consideration

- With respect to adverse events, are there any advantages of vemurafenib over dabrafenib for committee to note?
- Is it reasonable for committee to assume clinical equivalence between vemurafenib and dabrafenib? Or should committee use the results from the NMA for the comparison of cobimetinib and vemurafenib versus dabrafenib with the accompanying assumptions used in the modelling?
- Is there any scenario in which cobimetinib in combination with vemurafenib can be considered cost effective?