NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Trametinib in combination with dabrafenib 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, the ERG considered that in clinical practice some patients, for example those with lower volume or more indolent disease, or with minimal symptoms from their metastatic disease, may be treated with an immunotherapy instead of a BRAF inhibitor. Where are the BRAF inhibitors currently used in the treatment pathway? The company states that they are used first line and that less than 5% of people with BRAF V600 mutation-positive melanoma receive ipilimumab first line. Is this still the case in clinical practice? Following on from

this, would the combination only be used where BRAF inhibitors would otherwise be used, or in place of immunotherapy?

- The company draws the clinical effectiveness data from two trials (COMBI-d and COMBI-v) of people with previously untreated unresectable or metastatic BRAF V600 mutation-positive melanoma. However, the marketing authorisation for trametinib in combination with dabrafenib and the population defined in the scope are not limited to previously untreated patients. The ERG considered that there is no evidence of the effectiveness of trametinib in combination with dabrafenib 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 post failure of immunotherapy as first line, and would the relative benefit of adding trametinib to a BRAF agent be the same second line as first line?
- COMBI-d and COMBI-v included centres across Argentina, US, Canada and Europe. A combined total of 72 out of 1,127 patients (33 in COMBI-d and 39 in COMBI-v) were from UK centres. What is the committee's view on the generalisability of COMBI-v and COMBI-d to the UK clinical setting?
- COMBI-d and COMBI-v included fewer than 20 patients with brain metastases and all had an Eastern Cooperative Oncology Group (ECOG) performance of 0 or 1. Does the committee consider that this reflects the characteristics of patients treated in clinical practice in England?
- The COMBI-v trial is an open label, non-placebo controlled trial that did not have a blinded independent review of the radiological outcomes although the primary outcome was overall survival (OS). The ERG was unsure of what, if any, bias was caused by the trial design. What is the committee's view of the COMBI-v results?
- People in COMBI-v having vemurafenib monotherapy were allowed to switch treatment at planned interim analysis after the study was stopped for efficacy and a total 6% of people switched treatment. The ERG considered that treatment switching did not substantially impact on the OS results. What is the committee's view?

- COMBI-d was a placebo controlled double blinded study with a primary outcome of progression-free survival (PFS). The company used a later unplanned investigator analysis of PFS, not subject to independent review, in its cost effectiveness analysis. Is this reasonable?
- People in the trials were able to continue on therapy post progression if they were 'still benefiting from the study treatment'. The summary of product characteristics for the combination treatment states that 'treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity'. What would happen in clinical practice?
- What is the committee's view on the adverse event and quality of life data collected in the trial? Does it show a difference depending on the treatment taken?

Cost effectiveness

- The company presented a de novo partitioned survival model to assess the cost-effectiveness of trametinib in combination with dabrafenib. The ERG considered that the model produced counterintuitive results whereby the less effective the intervention was assumed to be at delaying progression, the more cost effective it became. This is because of the assumption that treatment is stopped at progression (limiting costs) but the risk of death is no different whether in the pre progression or post progression state. What is the Committee's view of the model design?
- The model is driven by OS estimates. The company used a 4 step extrapolation method to estimate long-term OS. The ERG considered that the company's methods led to implausible results in that at 5 years the survival in the monotherapy arm was less than in the melanoma cancer registry data. The ERG commented that the company had substantially underestimated survival in the monotherapy arm by overestimating the monthly hazard of death, and therefore had substantially underestimated the incremental cost-effectiveness ratio (ICER) for trametinib in combination with dabrafenib. What is the committee's view on the most appropriate method for modelling OS?
- The company used pooled OS estimates from the COMBI-d and COMBI-v trials in the model. The ERG considered that pooling data from a blinded placebo

controlled trial with data from an open-label, non-placebo controlled trial was not appropriate and underestimated survival in the monotherapy arms. Does the committee consider the pooling of the COMBI-v and COMBI-d trial data appropriate?

- The company used progression free survival (PFS) data to estimate treatment costs in both arms. The ERG considered that using PFS underestimates the costs of trametinib in combination with dabrafenib because over 25% of patients in both trials continued on treatment post progression, and that time to treatment discontinuation (TTD) provides a better estimation of costs. What is the committee's view on the most appropriate method for estimating treatment cost?
- The company assumed that patients receiving first-line treatment with trametinib in combination with dabrafenib have different post-study anti-cancer treatments from those whose first-line therapy was a BRAF inhibitor. The ERG commented that it could not statistically or clinically reason why post-study anti-cancer treatments were different across arms and considered that an equal post-study anti-cancer treatment cost and utility should be applied across all arms. What is the committee's view on the incorporation of post-study anti-cancer treatment costs and utilities?
- The company applied differential utility values for the PFS state depending on treatment arm. The ERG considered that there was no robust statistical basis for this assumption and that utility values should be applied to patients whilst 'on' treatment and 'off' treatment rather than based on progression status. What is the committee's preferred approach to incorporating utility values into the model?
- The results from the company's model showed that after agreed patient access schemes had been applied the deterministic ICERs for trametinib in combination with dabrafenib were £[redacted] and £[redacted] per QALY gained compared with dabrafenib and vemurafenib respectively. The ERG carried out a number of exploratory analyses, including:
    - changing the modelling of OS, which increased the ICERs to £[redacted] and £[redacted] per QALY gained compared with dabrafenib and vemurafenib respectively
    - changing the modelling of OS, using time to treatment discontinuation data to estimate treatment costs, incorporating equal post-study anti-cancer

treatments for the intervention and comparator therapies, and different utility values depending on whether people were on or off treatment (with no difference in utility between treatments). These changes increased the ICERs to £[redacted] and £[redacted] per QALY gained compared with dabrafenib and vemurafenib respectively

- all the above changes, and using COMBI-d trial data instead of pooled data from COMBI-d and COMBI-v to estimate effectiveness in the intervention and comparator arms, which increased the ICERs to £[redacted] and £[redacted] per QALY gained compared with dabrafenib and vemurafenib respectively.
- What is the committee's view on the most plausible ICER?

Other

- The company considered trametinib in combination with dabrafenib to be innovative in the management of advance melanoma. The reasons given by the company include the substantial efficacy gains, the reduction in the incidence of a number of skin toxicities associated with BRAF inhibitor therapy, and fewer unpleasant side effects. Does the committee consider trametinib in combination with dabrafenib to be an innovative therapy?
- The company stated that trametinib in combination with dabrafenib met all the criteria to be considered a life extending treatment at the end of life. Is the committee satisfied that all the criteria have been met, the estimates presented by the company are robust enough and the assumptions used in the model are plausible, objective and robust?

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 dabrafenib and trametinib within their marketing authorisations 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	Comments from the company	Comments from the ERG
Pop.	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma	In line with final NICE scope	The ERG noted that the scope states that if the evidence allows, consideration should be given to trametinib in combination with dabrafenib as a first-line therapy or after treatment with immunotherapy. However, all the patients recruited into the trials (COMBI-d and COMBI-v) were previously untreated. The trials included fewer than 20 patients with brain metastases and all had an ECOG performance of 0 or 1
Int.	Trametinib in combination with dabrafenib	Trametinib in combination with dabrafenib	In line with final NICE scope	The ERG commented that dabrafenib monotherapy is currently recommended by NICE as a treatment for advanced (unresectable or metastatic) melanoma but that trametinib monotherapy has not been appraised by NICE
Com.	• Dabrafenib • Vemurafenib	• Dabrafenib • Vemurafenib	In line with final NICE scope	The ERG commented that in clinical practice some patients with unresectable or metastatic

				BRAF V600 mutation-positive melanoma would be treated with an immunotherapy instead of a BRAF inhibitor and therefore that pembrolizumab and ipilimumab may also be relevant comparators.
Out.	• 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	In line with final NICE scope	The ERG noted that the company's submission contained information on all the relevant outcomes.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ERG, evidence review group; Pop, Population; BRAF, Protein of the mitogen-activated protein kinase pathway; Int, intervention; Com, comparators; Out, outcomes. Source: adapted from the company's submission, table 1				

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 Trametinib (Mekinist, Novartis Pharmaceuticals) is an inhibitor of MEK1 and MEK2 kinases. Trametinib inhibits the action of the abnormal BRAF protein, with the aim of slowing the growth and spread of the cancer. Dabrafenib (Tafinlar, Novartis Pharmaceuticals) is an orally bioavailable and selective inhibitor of BRAF V600 kinase activity. It aims to block the activity of mutant protein kinase causing the cancer cells stop growing and die.

2.3 Trametinib and dabrafenib have marketing authorisations in the UK, as monotherapies and in combination with each other, for treating adults with unresectable or metastatic melanoma with a BRAF V600 mutation. Both trametinib and dabrafenib are administered orally.

2.4 The company for trametinib and dabrafenib (Novartis Pharmaceuticals) has agreed patient access schemes with the Department of Health for each technology. Both schemes involve a single confidential discount applied to the list price of trametinib and dabrafenib (see Table 2). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Table 2 Technology and comparators

	Trametinib + dabrafenib	Dabrafenib	Vemurafenib
Marketing authorisation	Combination therapy for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	Monotherapy for adults with unresectable or metastatic melanoma with a BRAF V600 mutation	Monotherapy for adults with BRAF V600 mutation-positive unresectable or metastatic melanoma
Administration method and dose	2mg once daily of trametinib, combined with dabrafenib 150mg twice daily at full dose, until the patient no longer derives benefit or has unacceptable toxicity Oral	150 mg twice daily, until the patient no longer derives benefit or has unacceptable toxicity Oral	960 mg twice daily, until disease progression or unacceptable toxicity Oral
Acquisition cost	Trametinib 7 x 2mg tablets: £1,120; Dabrafenib 28 x 75-mg capsules: £1,400	28 x 75-mg capsules: £1,400	56 x 240mg tablets: £1,750
Average cost of a course of treatment (based on median length)	Average cost per course of treatment estimated by the company based on the list price is £129,210. This is based on full dose treatment with a median treatment duration of 11.8 months;	£1,400 per week based on the list price†	£1,750 per week based on the list price†

Abbreviations: BRAF, Protein of the mitogen-activated protein kinase pathway;

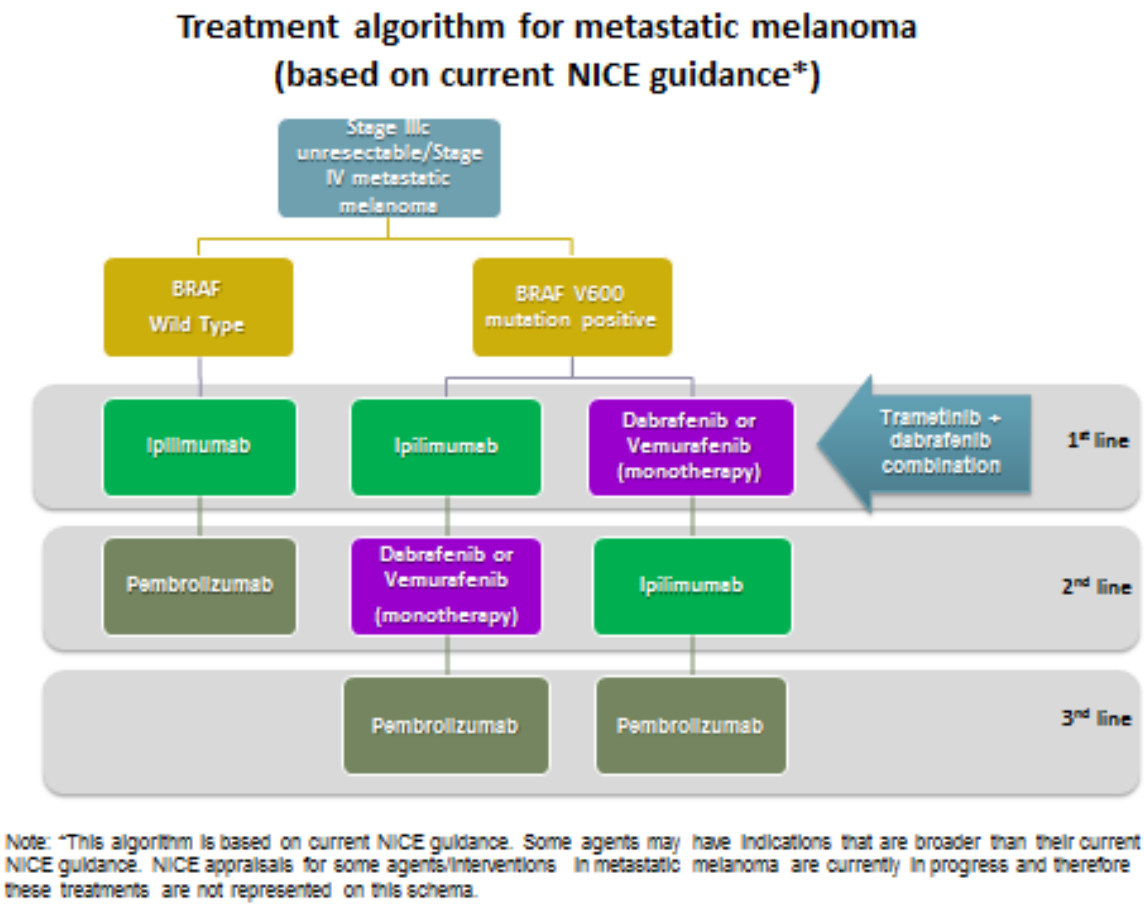
† Currently supplied to the NHS under an agreed patient access scheme; due to confidentially agreements, the detail of the scheme cannot be reported in this document

Source: British national formulary online (December 2015); European medicines agency; company's submission, table 6

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

2.5 Treatment options for metastatic melanoma include biological therapy, chemotherapy, radiotherapy or surgery but can depend on the person's BRAF mutation status and their treatment history. 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. NICE TA guidance 319 and 268 recommend ipilimumab, which is not a BRAF-targeted therapy, for untreated or previously treated 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 company suggests that trametinib in combination with dabrafenib could be used in place of the BRAF inhibitor monotherapies (see Figure 1).

Figure 1 Treatment pathway



Source: Company's submission, figure 2

3 Comments from consultees

3.1 Consultees broadly agreed with the treatment pathway. One noted that that around two-thirds of patients with the BRAF mutation are being diagnosed early, with low volume, slow progressing disease and these patients who are otherwise fit and well are more likely to be offered immunotherapy with either ipilimumab or pembrolizumab initially. Those with poorer prognosis, characterised by features including high volume disease, high serum LDH, rapid disease progression, poor performance status and multiple brain metastases will be offered BRAF inhibitors.

3.2 Two professional groups noted that dabrafenib in combination with trametinib should only be given by specialist melanoma oncologists in

secondary care. They commented that additional pharmacy time may be required in dispensing a combination therapy compared with a monotherapy, and that patients will discontinue treatment upon radiological disease progression, therefore repeat imaging will be necessary throughout the duration of treatment, at clinically appropriate intervals.

3.3 Two professional groups noted that patients with high levels of LDH and brain metastases at presentation generally have a worse prognosis and could be identified as a subgroup of interest.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company did a systematic literature review and identified 2 phase III clinical trials (COMBI-d [n=423] and COMBI-v [n=704]). Both trials investigated the effect of treatment with trametinib in combination with dabrafenib in people with a histologically confirmed stage IIC (unresectable) or stage IV (metastatic) melanoma who were BRAF V600E/K mutation-positive. The company also presented supportive evidence from a phase II trial (BRF113220 [n=162]). Further details of this trial can be found on page 58 and 59 of the company's submission.

COMBI-d

4.2 COMBI-d was a phase III, double-blind multicentre (103 centres across 14 countries, including centres in Australia, Canada, across Europe [including the UK] and the US) randomised controlled trial. The trial compared trametinib in combination with dabrafenib (150mg twice daily with trametinib 2 mg once daily, [n=211]) with dabrafenib monotherapy (150 mg twice daily with placebo control, [n=212]). Study treatment was continued until disease progression, death or unacceptable adverse events. The primary outcome was PFS that is, the time from randomisation to documented disease progression or death. The key secondary outcomes were OS that is, time from randomisation to death by

any cause, overall response rate (ORR) and adverse events. The exploratory outcome of health-related quality of life was measured using the EuroQol 5 dimension questionnaire (EQ-5D) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30).

COMBI-v

4.3 COMBI-v was a phase III, open label multicentre (across 28 countries, including centres in Argentina, Brazil, Canada, across Europe [including the UK] and the US) randomised controlled trial. The trial compared trametinib 2 mg once daily) in combination with dabrafenib (150mg twice daily [n=352]) with vemurafenib monotherapy (960 mg twice daily, [n=352]). Study treatment was continued until disease progression, death or unacceptable adverse events. The primary outcome was OS and key secondary outcomes were PFS, ORR and adverse events. The exploratory outcome of health-related quality of life was measured using EQ-5D and the EORTC-QLQ-C30.

Patient characteristics

4.4 The company reported that demographic disease characteristics and prognostic factors in both trials were generally well balanced between the treatment groups at baseline. However, in COMBI-v there were more men in the combination arm (59% compared with 51%) and more patients had ≥3 disease sites in the vemurafenib arm (50% compared with 43%). In COMBI-d, more people had visceral disease at baseline than in the combination arm (78% compared with 68%). Further details on patient characteristics can be found at section 4.5.2 in the company's submission.

ERG comments

4.5 The ERG reported that the company had identified all clinical trials relevant to the decision problem. It noted that COMBI-d and COMBI-v included centres in the UK (72 UK patients, 33 in COMBI-d and 39 in COMBI-v, out of 1,127). The ERG considered COMBI-d to be well designed and to have a low risk of bias. It reported that COMBI-v was of

good quality but noted that the trial was open-label, and did not include a placebo control or a blinded independent review of the secondary outcomes, which could lead to bias.

4.6 The ERG commented that patients in COMBI-d and COMBI-v were previously untreated and that there is no evidence for the use of trametinib in combination with dabrafenib as a second line treatment following immunotherapy. It also noted that the trials included fewer than 20 patients with brain metastases and that all had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1.

Clinical trial results

4.7 The company submitted primary and secondary outcome results from two time points:

- Pre-planned cut off (COMBI-d: August 2013; COMBI-v: April 2014)
- Final cut off (COMBI-d: January 2015; COMBI-v: March 2015)

A blinded independent review committee assessed the data of pre-specified analysis at the pre-planned cut off point. The company reported that the results were consistent with their observed results. A blinded independent review committee was not used at the final cut off point. Cross over was not permitted in COMBI-d. In COMBI-v, after the pre-planned cut off, the Independent Data Monitoring Committee recommended stopping the study early due to superior efficacy in the combination group. As a result the study protocol for COMBI-v was amended to allow crossover from vemurafenib to the combination therapy group.

Progression free survival

4.8 Results based on investigator assessment from COMBI-d showed, at final cut off, a median PFS of 11.0 months in the trametinib and dabrafenib group compared to 8.8 months in the dabrafenib monotherapy group (see Table 3). The company reported that this demonstrated a 33% reduction

in the risk of progression or death in those in the trametinib and dabrafenib combination group compared with those in the dabrafenib monotherapy group (hazard ratio [HR]=0.67; 95% confidence interval [CI]: 0.53 to 0.84; p=0.0004). Results from COMBI-v demonstrated similar efficacy of the trametinib and dabrafenib combination compared with vemurafenib monotherapy, with a median PFS of 12.6 months and 7.3 months respectively. The difference in risk between the groups was statistically significant (HR=0.61; 95% CI: 0.51 to 0.73; p<0.001) (see Table 3).

Table 3 Summary of PFS results in COMBI-d and COMBI-v at final cut off (Investigator analysis, ITT population)

	COMBI-d		**COMBI-v**	
	Trametinib + dabrafenib (n=211)	Dabrafenib (n=212)	Trametinib + dabrafenib (n=352)	Vemurafenib (n=352)
Progression free survival				
Event, n (%)	139 (66)	162 (76)	214 (61)	246 (70)
Median follow-up time, months	20	16	19	15
Median PFS, months	11.0	8.8	12.6	7.3
(95% CI)	(8.0 to 13.9)	(5.9 to 9.3)	(10.7 to 15.5)	(5.8 to 7.8)
HR (95% CI)	0.67 (0.53 to 0.84)		0.61 (0.51 to 0.73)	
p-value†	p=0.0004		p<0.001	

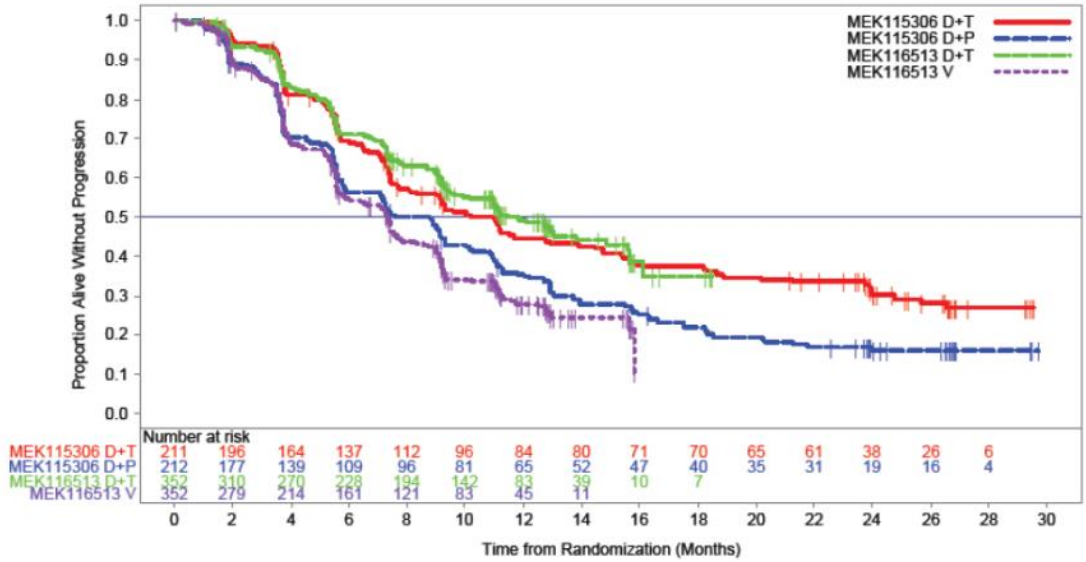
Abbreviations: CI, Confidence interval; HR, Hazard ratio; ITT, intention-to-treat; PFS, progression free survival

† Based on stratified log-rank test

Source: Company submission: tables 27 and 37

4.9 The company provided Kaplan Meier analysis based on investigator-assessed PFS in the ITT population for both trials (see Figure 2).

Figure 2 Kaplan Meier analyses of progression free survival based on investigator assessment in COMBI-d[1] (MEK115306) and COMBI-v[2] (MEK226513), ITT population



[1] January 2015 cut off
[2] April 2014 cut off
Source: company's submission, figure 27, page 165

Overall survival

4.10 The company reported statistically significant and clinically meaningful differences in OS between the trametinib and dabrafenib combination group and the monotherapy groups. In COMBI-d median OS was 25.1 months in the combination group compared with 18.7 months in the dabrafenib monotherapy group (HR=0.71; 95% CI: 0.55 to 0.92, p=0.011). In COMBI-v median OS was 25.6 months in the combination group compared with 18.0 months in the vemurafenib group (HR=0.66; 95% CI: 0.53 to 0.81, p<0.001). After pre-planned cut off, patients in the COMBI-v trial were allowed to crossover treatment. At the final cut off point, 21 patients had switched from vemurafenib to trametinib in combination with dabrafenib. The company noted that the switching of treatments may have impacted on the OS gain. It adjusted for crossover using the Rank Preserving Structural Failure Time (RPSFT) method, which showed an

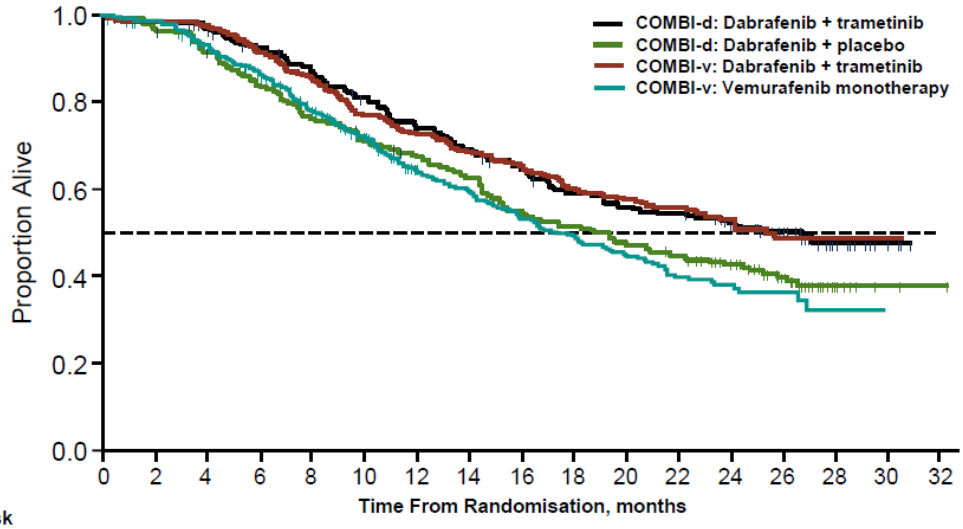
adjusted HR of 0.63 (95% CI: 0.50 to 0.79). The company presented Kaplan-Meier curves for both trials (see Figure 3). The company also reported that the OS benefit was observed despite a greater proportion of people in the comparator groups receiving subsequent anti-cancer treatment after progression compared with those in the trametinib and dabrafenib combination groups (see company's submission, Tables 30 and 36).

Table 4 Summary of OS results in COMBI-d and COMBI-v (ITT population)

	COMBI-d		**COMBI-v**	
	Trametinib + dabrafenib (n=211)	Dabrafenib (n=212)	Trametinib + dabrafenib (n=352)	Vemurafenib (n=352)
Overall survival				
Median follow-up time, months	20.0	16	19	15
Median, months	25.1	18.7	25.6	18
(95% CI)	(19.2 to NR)	(15.2 to 23.7)	(22.6 to NR)	(15.6 to 20.7)
HR (95% CI)	0.71 (0.55 to 0.92)		0.66 (0.53 to 0.81)	
p-value	p=0.011		p<0.001	
1-year OS % (95% CI)	74 (67 to 79)	68 (61 to 74)	73 (68 to 77)	64 (59 to 69)
2-year OS % (95% CI)	51 (44 to 58)	42 (35 to 49)	51 (45 to 57)	38 (32 to 44)
% crossover	Not applicable		21 / 352 (6%)	
RPSFTM-adjusted HR (95% CI)	Not applicable		0.63 (0.50 to 0.79)	

Abbreviations: Ci, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reached; OS, overall survival; RPSFTM, Rank Preserving Structural Failure Time Model
Source: Company's submission, table 29 and 35

Figure 3 Kaplan Meier curve for overall survival in COMBI-d[1] and COMBI-v[2] (ITT population)



Number at risk																	
COMBI-d D + T	211	208	200	187	174	159	144	135	124	112	106	103	88	53	21	3	0
Dabrafenib + placebo	212	206	191	175	159	147	138	127	111	104	95	88	70	42	10	2	1
COMBI-v D + T	352	342	336	311	286	260	245	230	217	198	173	128	68	38	16	5	0
Vemurafenib	352	341	315	286	252	231	201	187	166	152	129	88	46	28	7	0	0

[1] January 2015 cut off

[2] March 2015 cut off

Source: Company submission, figure 12, p 106

Overall response rates and duration of response

4.11 Overall response rates (ORR) and duration of response are summarised in Table 5. ORR was defined as the proportion of patients with complete or partial response. At the final cut-off point, COMBI-d results showed more patients had achieved a complete response or partial response in the trametinib and dabrafenib combination group (ORR=69%; CI: 61.8 to 74.5) than in the dabrafenib monotherapy group (ORR=53%; CI: 46.3 to 60.2) (p=0.0014). Results from COMBI-v showed that the ORR was significantly higher in the trametinib and dabrafenib combination group (66%; CI: 60.4 to 70.6) compared with the vemurafenib monotherapy group (53%; CI: 47.5 to 58.2) (p=0.0008).

Table 5 Overall response rates and duration of response of investigator analysis from COMBI-d and COMBI-v (ITT population)

	COMBI-d	COMBI-v

	Trametinib + dabrafenib (n=211)	Dabrafenib (n=212)	Trametinib + dabrafenib (n=352)	Vemurafenib (n=352)
Overall response rate				
ORR (CR + PR), n (%)	144 (69%)	112 (53%)	231 (66%)	186 (53%)
(95% CI)	(61.8, 74.8)	(46.3, 60.2)	(60.4, 70.6)	(47.5, 58.2)
p-value	p=0.0014		p=0.0008	
Duration of response				
Median, months	12.9	10.6	13.8	8.5
(95% CI)	(9.4–19.5)	(9.1–13.8)	(11.2-18.1)	(7.4-9.7)
Abbreviations: CI, confidence interval; Complete response, ITT, intention to treat; ORR, overall response rate; Partial response Source: Company's submission, table 31 and 38				

ERG comments

4.12 The ERG agreed with the company that trametinib in combination with dabrafenib demonstrated greater clinical effectiveness compared with dabrafenib and vemurafenib monotherapies. The ERG agreed with the company's conclusion that the PFS results at the final cut off points were consistent with the results from the pre-planned cut off points. The ERG considered that stopping the COMBI-v trial early did not appear to have biased the efficacy results, and that the OS data were very mature and consistent with the findings from the pre-planned April 2014 data cut. It noted that around 6% of patients in the vemurafenib arm crossed over to the combination arm, and considered that this would not substantially impact on the OS results.

Health related quality of life

4.13 The company presented health related quality of life results from both trials using two measures, EQ-5D and EORTC-QLQ-30 (full results can be found in the company's submission, page 107-111 and 116-120). For COMBI-d, baseline EQ-5D scores were similar between treatment arms (0.765 for trametinib in combination with dabrafenib and 0.730 for dabrafenib monotherapy). There was a statistically significant difference in results favouring the combination arm at week 16 but no other statistically significant results were reported. EORTC-QLQ-30 results for global health were significantly better at weeks 8, 16 and 24 in the combination therapy group compared with the dabrafenib monotherapy group ($p<0.05$). For COMBI-v, baseline EQ5D scores were similar between treatment groups (0.751for the combination arm and 0.715 for vemurafenib monotherapy). For all assessments, the differences between scores for the two treatment groups were significantly better for the combination arm. The company reported that EORTC-QLQ-30 global health scores were significantly better and clinically meaningful for patients in the combination therapy arm compared with vemurafenib monotherapy ($p<0.05$).

ERG comments

4.14 The ERG had some concerns about the extent to which the collected EQ5D data may be considered representative of the experience of the whole melanoma population. For example, it observed that in the trametinib in combination with dabrafenib arms of COMBI-d and COMBI-v the utility scores at week 40 and week 48 were higher than those at baseline (+0.01 and +0.07 respectively). Similarly, data from both trials showed that the utility scores at the point of disease progression for patients receiving the combination treatment were higher than those at baseline (+0.04 and +0.06 respectively). The ERG considered that these observations may be because only patients who felt well completed the questionnaires. The ERG also commented that the lack of study blinding in COMBI-v may have influenced the scores reported by patients.

Adverse effects of treatment

4.15 The company presented adverse events based on COMBI-d and COMBI-v (summarised in Table 6 and Table 7). It reported that trametinib in combination with dabrafenib has a well-characterised safety profile that is manageable with appropriate interventions as specified in the summaries of product characteristics.

4.16 The company stated that in COMBI-d, adverse events leading to treatment discontinuation, dose reductions or dose interruptions were more common in the combination arm compared with the dabrafenib monotherapy arm, whereas in COMBI-v the proportions were generally similar between the combination arm and the vemurafenib monotherapy arm. The company reported that approximately half of the adverse events experienced by patients receiving trametinib and dabrafenib combination treatment were mild-to-moderate in severity (Grades 1 and Grade 2). In both studies, the rates of Grade 3/4 adverse events were higher in the monotherapy arms than in the combination arms (50% and 45% in COMBI-d; 57% and. 66% in COMBI-v). Pyrexia and hypertension were the most common Grade 3/4 events occurring with trametinib and

dabrafenib combination therapy in both studies. Although the combination of trametinib and dabrafenib resulted in a higher incidence of some adverse events relative to the monotherapies (most notably pyrexia), fewer skin-related toxicities were observed.

Table 6 Summary of adverse events

	Trametinib + dabrafenib (n=209)	**Dabrafenib (n=211)**	**Trametinib + dabrafenib (n=350)**	**Vemurafenib (n=349)**
Median follow-up time, months	20	16	19	15
Any AE, n (%)	**203 (97)**	**205 (97)**	**345 (99)**	**345 (99)**
AEs leading to permanent discontinuation of study treatment	24 (11)	14 (7)	55 (16)[d]	48 (14)
AE leading to dose reduction	59 (28)	29 (14)	112 (32)	124 (36)
AE leading to dose interruption	118 (56)	78 (37)	163 (47)	163 (47)
Any SAE, n (%)	**88 (42)**	**78 (37)**	**151 (43)**	**136 (39)**
Fatal SAEs	5 (2)	1 (<1)	4 (1)	4 (1)
Fatal SAEs related to study treatment	0	1 (<1)	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event
Source: Company's submission, Table 51, page137

Table 7 Summary of common adverse events in COMBI-d and COMBI-v

	COMBI-d				COMBI-v			
	Trametinib + dabrafenib		Dabrafenib		Trametinib + dabrafenib		Vemurafenib	
Median follow-up time, months	20		16		19		15	
Grade	**Any**	**G3/G4**	**Any**	**G3/G4**	**Any**	**G3/G4**	**Any**	**G3/G4**
Any AE, n (%)	203 (97)	95 (45)	205 (97)	106 (50)	345 (99)	197 (57)	345 (99)	232 (66)
Pyrexia	119 (57)	15 (7)	69 (33)	4 (2)	193 (55)	16 (5)	74 (21)	2 <1)
Hypertension	52 (25)	12 (6)	33 (16)	13 (6)	103 (29)	54 (15)	82 (23)	33 (9)
SCC	3 (1)	3 (1)	9 (4)	9 (4)	2 (<1)	2 (<1)	21 (6)	20 (6)
SCC of skin	2 (1)	2 (1)	11 (5)	11 (5)	3 (<1)	3 (<1)	32 (9)	32 (9)
Keratoacanthoma	1 (<1)	1 (<1)	4 (2)	4 (2)	2 (<1)	2 (<1)	35 (10)	35 (10)
Basal cell carcinoma	7 (3)	6 (3)	13 (6)	13 (6)	8 (2)	6 (2)	3 (<1)	3 (<1)
Rash	56 (27)	0	46 (22)	2 (<1)	84 (24)	3 (<1)	150 (43)	30 (9)
Rash maculopapular	12 (6)	0	8 (4)	1 (<1)	13 (4)	2 (<1)	28 (8)	13 (4)
Neutropenia	20 (10)	7 (3)	4 (2)	1 (<1)	33 (9)	18 (5)	6 (2)	3 (<1)
Anaemia	13 (6)	6 (3)	20 (9)	9 (4)	26 (7)	7 (2)	21 (6)	4 (1)
AST increased	28 (13)	7 (3)	9 (4)	2 (<1)	42 (12)	5 (1)	46 (13)	9 (3)
ALT increased	28 (13)	5 (2)	12 (6)	1 (<1)	49 (14)	9 (3)	61 (17)	15 (4)
GGT increased	5 (2)	3 (1)	5 (2)	2 (<1)	38 (11)	19 (5)	33 (9)	17 (5)
Ejection fraction decreased	12 (6)	3 (1)	7 (3)	4 (2)	33 (9)	13 (4)	1 (<1)	0
Hyponatraemia	4 (2)	3 (1)	2 (<1)	2 (<1)	17 (5)	16 (5)	12 (3)	8 (2)
Arthralgia	54 (26)	2 (<1)	66 (31)	0	93 (27)	3 (<1)	182 (52)	15 (4)

Abbreviations: AE, adverse events; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; G3, Grade 3 event; G4, Grade 4 event; SCC, Squamous cell carcinoma; GGT, Gamma glutamyl transferase

Source: Company's submission, table 53, p 140

ERG comments

4.17 The ERG agreed with the company that the incidences of skin-related adverse events occurred less frequently in patients treated with trametinib in combination with dabrafenib compared with patients treated with a BRAF inhibitor. It also acknowledged that the studies showed a slightly lower number of grade 3 and 4 events for patients receiving the combination treatment compared with the monotherapies. However, the ERG commented that the proportion of adverse events leading to permanent discontinuation of study treatment, dose reductions or dose interruption was higher in the combination arm than in the dabrafenib arm of the COMBI-d study.

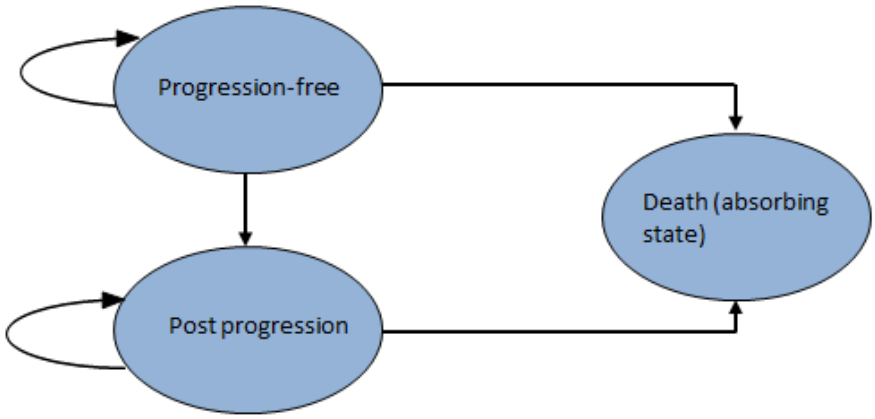
5 Cost-effectiveness evidence

Model structure

5.1 The company presented a de novo partitioned survival model to assess the cost-effectiveness of trametinib in combination with dabrafenib in people with BRAF V600 mutation-positive unresectable or metastatic melanoma. The perspective was that of the NHS and Personal Social Services. The time horizon of the model was life time (30 years), the cycle length was 1 week and half-cycle correction was not applied. Costs and outcomes were discounted at 3.5% per year.

5.2 The model included 3 states: progression-free, post progression and death (see Figure 4). The company assumed that participants entered the model in the progression-free state and had treatment with trametinib in combination with dabrafenib or one of the BRAF inhibitor monotherapies (dabrafenib or vemurafenib). Transition between states was derived from response to treatment and risk of disease progression or death. Patients that transitioned to a post-progression state were assumed to discontinue therapy and stayed in that state until transitioning to death. Progression of disease was defined based on RECIST v1.1.

Figure 4 Company's model structure



Source: Company's submission, figure 28

ERG comments

5.3 The ERG noted that the model structure had been used in previous NICE appraisals in this disease area, and had been previously critised by the ERG because reductions in the assumed effectivenss of the intevention led to an increase in its cost effectiveness. The ERG noted that the same counterintuative results applied to the present model and therefore that the model structure was inappropriate. The ERG explained that the issue is exemplified by the scenario analysis undertaken by the company in which the hazard ratios for progression at the end of the trial period are assumed to be equal for both arms, rather than lower for the combination arm as in the base case analysis (see section 5.20). This assumption effectively makes combination treatment less effective at delaying progression than monotherapy with dabrafenib or vemurafenib compared with the base case analysis yet generates a lower ICER. The ERG further commented that it is not possible to explore how changes in the assumption of effectivenss of treatment impact on the ICER.

5.4 The ERG commented that the company's model relates to patients who receive BRAF inhibitor therapy as a first line treatment but that the treatment pathway does not reflect current clinical practice post

progression. The ERG's clinical advice suggests that patients who are well enough to start a second line therapy would be offered pembrolizumab in current NHS pratice, which is not reflected in the company's model. The ERG commented that this may cast doubt on the OS estimates generated by the model.

Model details

Modelling of clinical effectiveness data

The clinical effectiveness estimates for each of the treatment groups were taken from pooled PFS and OS failure times at the final cut off points from the COMBI-v (March 2015) and COMBI-d (January 2015) trials. The company stated that the individual trials were not sufficient enough in power to calculate the area-under the curve (AUC) and that pooling the data increased the level of precision in the estimates of treatment effect. The company stated that the trial designs and populations were similar in COMBI-d and COMBI-v and could be pooled. It further commented that while there were no controlled trials directly comparing dabrafenib and vemurafenib, a comparison of efficacy results from the 2 phase III studies (BREAK-3 and BRIM-3) indicated that their efficacy is very similar. The company commented that they did not pool the safety data and the pre-progression data in dabrafenib and vemurafenib because they had distinct profiles.

Long-term extrapolation

To estimate the long term survival of trametinib in combination with dabrafenib, the dabrafenib, the company extrapolated PFS and OS beyond the follow up period. The period. The company noted that goodness of fit during the trial period may not be the most not be the most accurate estimator for long-term projection of treatment effect. To estimate effect. To estimate the long-term PFS and OS, the company used Kaplan-Meier analysis until Meier analysis until a predetermined break point, beyond which a long-term linear trend was term linear trend was evident. For PFS there was an assumption of constant constant hazards/exponential distribution applied to each arm and an assumption that assumption that observed PFS benefits would continue beyond the trial follow up (see

Figure 5).For OS the company used Kaplan Meier data until a predetermined breakpoint, after which an assumption of constant hazards was applied until year 5. The company stated that if the constant hazards were used for the duration of lifetime, survival projections were inconsistent with known survival data from the American Joint Commission on Cancers Commission on Cancers (AJCC) Melanoma Registry. Accordingly, the company combined company combined exponential extrapolation of constant hazards with long-term survival long-term survival data from the AJCC with case-mix adjustments. Case mix adjustments mix adjustments were made by applying a restricted cubic splines paramedic survival paramedic survival distribution for survival in the AJCC with Kaplan Meier trial data for trial data for each arm and by melanoma stage. General population mortality, matched by age mortality, matched by age and gender, was added to the AJCC rates after 20 years to account 20 years to account for increased risk of death in the population (see

5.5 Figure 5).

Figure 5 Long-term projections of PFS and OS for trametinib + dabrafenib and BRAF inhibitor monotherapy based on the Kaplan-Meier curves plus exponential projection after the break point with OS converging to case-mix adjusted AJCC

[redacted]

Source: company's submission, figure 37, page 200

Transition probabilities

5.6 Area under the curve was used to estimate mean PFS and OS. The difference between the two curves provided an estimate of the mean time alive following disease progression.

Utility values

5.7 The company assigned utility values to each of the health states in the model (see Table 8) using EQ5D data from COMBI-v and COMBI-d. The model assumes that within each health state the quality of life is constant over time, i.e. a single utility value applies to that health state. Adverse events were indirectly incorporated in the model as utility data were taken directly from the trials.

Table 8 Utility values used in base case model

Treatment	Mean	SE	Source
PFS			
Trametinib + dabrafenib	0.837	0.004	Weighted average of all pre-progression utility assessments (excluding baseline) among trametinib + dabrafenib patients in pooled dataset.
Vemurafenib	0.746	0.009	Calculated based on estimated utility for trametinib + dabrafenib (0.8369) and difference in weighted average of all pre-progression utilities assessments (excluding baseline) for vemurafenib vs. trametinib + dabrafenib in COMBI-v (-0.0908).COMBI-v
Dabrafenib	0.789	0.011	Calculated based on estimated utility for trametinib + dabrafenib (0.8369) and difference in weighted average of all pre-progression utilities assessments (excluding baseline) for dabrafenib vs. trametinib + trametinib in COMBI-d (-0.0479).COMBI-d
PPS	0.697	0.012	Calculated by pooling the average of all post-progression assessments from COMBI-d (0.6998), and COMBI-v (0.6953) using random effects meta-analysis.
Abbreviations: PPS, post-progression survival; SE, standard error Source: Company's submission, table 88			

Model resource use

5.8 The model included all data on healthcare resource use associated with treatment and disease progression. The company used the UK MELODY study (a study of resource utilisation in 220 people with melanoma) to inform UK clinical practice in melanoma treatment and the basis for costing additional resource use in pre- and post-progression health states. Costs were inflated to present price levels. Discounting of 3.5% was applied to all costs on an annual basis. The company did not include screening costs for BRAF mutation; however, it noted that it does not make a difference to the model because it is not included as a resource cost in either the comparator or intervention arm. The model included post-study anti-cancer treatment costs in the model. These were calculated as a weighted sum of the expected total post-study anti-cancer treatment cost per patient progressing in the trials. The model only incorporated costs of treating adverse events which the company

determined were likely to have the greatest impact on NHS resource. This was derived by selecting those grade 3 and above adverse events with an incidence of ≥ 5% in either arm of COMBI-v or COMBI-d (see Table 9 and Table 10).

Table 9 Incidence of G3/4 AEs >= 5% in any arm

Grade 3+ Adverse Event	COMBI-v		COMBI-d	
	Trametinib + Dabrafenib	Vemurafenib	Trametinib + Dabrafenib	Dabrafenib
N (safety population)	350	349	209	211
Hypertension	15.4%	9.5%	5.7%	6.2%
Rash	0.9%	8.6%		
Squamous cell carcinoma*	1.4%	14.9%	2.4%	9.5%
Keratoacanthoma	0.6%	10.0%	-	-
Pyrexia	-	-	7.2%	2.4%
Basal cell carcinoma	-	-	2.9%	6.2%
Abbreviations: AE, adverse events; SCC, Squamous cell carcinoma *combines SCC and SCC of the skin in estimation Source: Company's submission, table 93, page 213				

Table 10 Costs associated with treated individual adverse events in the model

Adverse Event*	Cost per Event, £	
	Mean	SE†
Hypertension	1,438	359
Pyrexia	1,160	290
Rash	363	90
Squamous cell carcinoma	1,308	327
Basal cell carcinoma	1,308	327
Keratoacanthoma	1,308	327
G3+ AEs selected based on the criteria of ≥5% incidence in either treatment arm of COMBI-V or COMBI-D. Abbreviations: SE, standard error †SE assumed to be 50% of base case value Source: Company's submission table 95, page 214		

ERG comments

The modelling of clinical effectiveness data

5.9 The ERG agreed with the company that there is clinical evidence showing equivalent efficacy of dabrafenib and vemurafenib. The ERG commented that there were similarities in the trial designs and patient populations, but that COMBI-d was blinded and placebo controlled, while COMBI-v was neither blinded and no placebo control was used. The ERG commented that pooling data from a high quality blinded trial with data from a potentially biased trial may reduce the reliability of the estimates. The ERG noted that by pooling the data the company had not taken into account the potential for trial design bias. The ERG did not consider that pooling the data would increase the accuracy of the AUC analysis, as the Kaplan-Meier curves in COMBI-v and COMBI-d were almost identical. The ERG noted that the two trials have different survival profiles and it would not be appropriate to pool the data. It considered that the results from the high quality blinded, placebo controlled trial were more likely to show the true effectiveness of dabrafenib and vemurafenib, if their clinical equivalence was accepted. The ERG noted that there were clear differences in the OS of dabrafenib and vemurafenib from month 17 (see company's submission, figure 26). By using the pooled data, the ERG commented that the model provides a lower estimate of OS than if only COMBI-d data has been used.

Long term extrapolation

5.10 The ERG agreed with the company that using AJCC data in the long term extrapolation is an acceptable approach to estimate long term OS. The ERG did not agree with the company that a constant hazard should be applied after a breakpoint in the long term extrapolation. It considered that it was preferable for all of the trial data to be used rather than extrapolation over a period for which data exists. The ERG amended the model to reflect this.

5.11 The ERG did not consider that the company had appropriately extrapolated long term OS. It noted that the constant mortality hazards were not applied up to year 5, but up to month 30 (trametinib in combination with dabrafenib) or month 31 (monotherapy). The monthly mortality hazards declined in both arms consistently until they converged with the mortality hazards at year 5. The ERG commented that this underestimates the survival in the monotherapy arm and produces counterintuitive results. The ERG further explored the differences between monthly hazard rates over 5 years between the AJCC and the company results (see figure 7, ERG report). The ERG suggested that applying AJCC registry survival data from month 27 onwards for both arms would be more appropriate.

Figure 6 Company projected OS to 5 years compared with the AJCC registry data survival curve

[redacted]

Source: ERG report, figure 7

5.12 The ERG's alternative approach to modelling OS used the Kaplan-Meier data directly from the trials until month 27. From month 27, the ERG

suggested using mortality hazard rates from the AJCC to year 20, and then population mortality rates (adjusted by a mortality multiplier of 1.4) to year 30. The ERG also considered that using COMBI-d data rather than the pooled data from COMBI-d and COMBI-v, provided a more robust estimate of the difference in OS.

Figure 7 Company and ERG revised OS projections

[redacted]

Source: ERG report, figure 9

5.13 The ERG noted that the mean time for patients to continue to receive treatment post-investigator assessed progression was over 200 days in the trametinib in combination with dabrafenib group. The ERG considered that PFS is a poor proxy for time on treatment and treatment costs and that time to treatment discontinuation (TTD) would provide a more accurate measure. The ERG considered that differences in TTD in the monotherapy arms of COMBI-d and COMBI-v may be explained by the differences in trial design, notably the blinding.

Model resource use

5.14 Using TTD data, the ERG estimated that the total cost of treatment for trametinib in combination with dabrafenib increased from £[redacted]

(company's base case) to £320,153 (ERG's estimate). The ERG estimated that the total costs for dabrafenib and vemurafenib also rose from £[redacted] to £170,405 for dabrafenib; and from £[redacted] to £176,803 for vemurafenib). The ERG also noted that the TTD may be affected by the availability of pembrolizumab and ipilimumab, which may result in an overestimation of time on treatment in both the company's and the ERG's results.

5.15 The ERG did not agree that post-study anti-cancer therapy costs were different between the treatment arms. The ERG suggested that a simple average of the post-study anti-cancer therapy costs should be applied. The ERG noted that the company's post-study anti-cancer therapy costs did not represent the current clinical pathway as less than 7% of patients in COMBI-d and COMBI-v received pembrolizumab.

Utility values

5.16 The ERG noted that utility values used in the model were derived from the full study population and considered that data from European patients would provide a more representative estimate of utility. The ERG also considered the use of utility values from COMBI-v to be inappropriate considering the open label design of the trial and commented that it did not believe there was a statistical reason to apply different utility values to dabrafenib and vemurafenib monotherapies.

5.17 The ERG commented that the adverse event data from COMBI-d did not demonstrate that treatment with trametinib in combination with dabrafenib was more tolerable than treatment with dabrafenib monotherapy. The ERG highlighted that there were a greater number of adverse events that led to discontinuation of treatment, dose reduction, dose interruption and a fatal serious adverse events in the trametinib in combination with dabrafenib arm compared with the dabrafenib monotherapy arm. The ERG did not consider that the adverse event data supported a higher utility value for those treated with trametinib in combination with dabrafenib compared to dabrafenib or vemurafenib monotherapy.

5.18 The ERG considered that it would be more meaningful to apply utility values that are related to being ‘on’ or ‘off’ study treatment as determined by the TTD data. The ERG also considered that the utility values used in the model should reflect declining utility with age. The ERG applied a decrement for age in its model adjustments.

Company's base-case results and sensitivity analysis

5.19 The company presented cost effectiveness results based on the list prices of the intervention and comparator technologies. The company stated that because these results do not incorporate the confidential patient access schemes, they are not reflective of the actual cost to the NHS. Results incorporating the patient access schemes instead of the list prices are presented in section 5.21 below.

Company scenarios

5.20 The company did deterministic sensitivity analysis varying the assumptions in the model and based on the list prices of the intervention and comparator technologies (full details are presented in the company submission from page 230). The results were sensitive to the time horizon of the model, with a longer time horizon reducing the ICERs for trametinib and dabrafenib combination therapy compared with the monotherapies. The company also reported that assuming no continuing benefit for PFS beyond trial follow up reduced the ICERs (i.e. it was assumed that the hazard for PFS in the combination arm was constant throughout the projection period [HR = 0.694]).

ERG exploratory analyses

5.21 Using the company’s model, the ERG presented deterministic cost effectiveness results based on the confidential PAS discounted prices of the intervention and comparator technologies. Results showed that trametinib in combination with dabrafenib was associated with a greater number of quality adjusted life years (QALYs) compared with the monotherapies (1.345 more QALYs than vemurafenib and 1.297 more

QALYs than dabrafenib) and an increased cost (£[redacted] higher than vemurafenib and £[redacted] than dabrafenib). The incremental cost effectiveness ratio (ICER) for trametinib in combination with dabrafenib compared with dabrafenib monotherapy was £[redacted] per QALY gained and £[redacted] per QALY gained compared with vemurafenib.

5.22 The ERG made several amendments to the company's model:

- Use of TTD data to estimate study treatment costs (see sections 5.13 and 5.14)
- Use of equal post-study anti-cancer treatments for the intervention and comparator therapies (see section 5.15)
- Application of on and off treatment utility values relating to European patients and adjusted for age (see sections 5.16 to 5.18)
- Application of ERG method for estimating OS (see section 5.12)
- Use of COMBI-d trial data (instead of pooled data) and application of the ERG preferred method for estimating OS (see section 5.9).

5.23 The ERG reported that each amendment increased the ICER for trametinib in combination with dabrafenib compared with dabrafenib and vemurafenib monotherapies. Taking into account the combined effect of the amendments increased the ICER to £[redacted] per QALY gained compared with dabrafenib, and £[redacted] per QALY gained compared with vemurafenib. The results of the ERG's analyses are summarised in Table 11.

Table 11 ERG exploratory analyses (after patient access schemes are applied)

Model scenario	Trametinib + dabrafenib compared with dabrafenib				Trametinib + dabrafenib compared with vemurafenib			
	Cost	QALY	Life years	ICER £/QALY	Cost	QALY	Life years	ICER £/QALY
A. Company base case	[redacted]	**1.297**	**1.653**	[redacted]	[redacted]	**1.345**	**1.653**	[redacted]
ERG's revisions								
R1) TTD data for on treatment costs	[redacted]	1.297	1.653	[redacted]	[redacted]	1.345	1.653	[redacted]
R2) Equal PSACT costs	[redacted]	1.297	1.653	[redacted]	[redacted]	1.345	1.653	[redacted]
R3) Application of on and off treatment utilities and age related decrement with European patient values	[redacted]	1.187	1.653	[redacted]	[redacted]	1.167	1.653	[redacted]
R4) Application of ERG OS amendments	[redacted]	0.878	1.050	[redacted]	[redacted]	0.925	1.050	[redacted]
R5) Use of COMBI-d data for OS with ERG amendments	[redacted]	0.75	0.866	[redacted]	[redacted]	0.797	0.866	[redacted]
B. Base case + (R1:R2)	[redacted]	1.297	1.653	[redacted]	[redacted]	1.345	1.653	[redacted]
C. Base case + (R1:R3)	[redacted]	1.187	1.653	[redacted]	[redacted]	1.167	1.653	[redacted]
D. Base case + (R1:R4)	[redacted]	0.794	1.050	[redacted]	[redacted]	0.794	1.050	[redacted]
E. Base case + (R1:R3, R5)	[redacted]	**0.672**	**0.866**	[redacted]	[redacted]	**0.672**	**0.866**	[redacted]

Abbreviations: ERG, evidence review group; ICER, incremental cost effectiveness ration; Inc, incremental; OS, overall survival; PAS, patient access scheme; PSACT, post-study anti-cancer treatment; QALY, quality adjusted life year; R, Revision; TTD, time to treatment discontinuation

Source: adapted from ERG report, confidential appendix, tables 1 and 2

Innovation

5.24 The company included the following justifications for considering trametinib in combination with dabrafenib to be innovative:

- It has shown substantial efficacy gains with significant and clinically meaningful improvements
- It reduces the incidence of a number of skin toxicities associated with BRAF inhibitor therapy
- It has shown a reduction in the unpleasant side effects and uncomfortable disease-associated symptoms
- It may allow patients to spend quality time with their family and friends during times when the condition is stable and/or under control.

6 End-of-life considerations

6.1 The company submitted evidence that trametinib in combination with dabrafenib should be considered under the 'end-of-life' criteria (Table 12

Table 12 End-of-life considerations

Criterion	Data available	Source
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS: Dabrafenib monotherapy = 18.7 months (CI: 15.2 to 23.7; n=212) Vemurafenib monotherapy = 18.0 months (CI: 15.6 to 20.7; n=352) Dabrafenib monotherapy = 13.6 months (CI:16.7 to 24.4; n=X) Vemurafenib monotherapy = 18.0 months (CI:12.0 to 15.4; n=)	COMBI-d COMBI-v BREAK-3 BRIM3
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months,	Median OS gain: Trametinib + dabrafenib compared to dabrafenib = 6.4 months Trametinib + dabrafenib compared to vemurafenib = 7.6 months	COMBI-d COMBI-v

compared with current NHS treatment		
The treatment is licensed or otherwise indicated for small patient populations	The maximum number of patients covered by the therapeutic indication for trametinib in combination with dabrafenib therapy (adults with unresectable or metastatic melanoma with a BRAF V600 mutation) is estimated to be 992 cases per annum in England.	Company's submission, table 8

ERG comment

6.2 The ERG agreed with the company that median OS data from the BRAF inhibitor monotherapy arms of the four main trials (BREAK-3COMBI-d, BRIM-3 and COMBI-v) estimated that patients with advanced (unresectable or metastatic) melanoma had a life expectancy of less than 24 months (range 13.6 months to 20.1 months). It also noted that in the company's economic analyses mean life expectancy for patients receiving BRAF inhibitor monotherapy is estimated to be about 3 years. Using the ERG's preferred approach to OS modelling, the mean life expectancy is about 4 years.

7 Equality issues

7.1 No equality issues were raised during the scoping process. The company stated in its submission that it had not identified any equality issues related to treatment with trametinib in combination with dabrafenib.

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

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002604/WC500196276.pdf