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Single technology appraisal

Trametinib in combination with dabrafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID661]

Company evidence submission

Novartis Pharmaceuticals UK Limited

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		Yes	01/12/2015

All cost-effectiveness estimates incorporate the treatment and comparators at list prices (due to existing *confidential* PAS which are in place), and are therefore not reflective of the actual cost to the NHS. The confidential PAS addendum presents results incorporating the actual or estimated drug acquisition costs incorporating the discounts.

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1. Executive summary

Background to the Condition

Melanoma is an aggressive form of skin cancer arising from the malignant transformation of melanocytes that may spread to involve any organ. The incidence of melanoma is increasing faster than most other types of cancer. Approximately 13,000 new cases of melanoma were diagnosed in England in 2013, and nearly 2,000 people died from the disease.[1; 2] Melanoma disproportionately affects a younger population compared to other cancers[3] and therefore has significant impact for patients, their family and wider society. Prognosis for patients who develop metastatic melanoma is poor; historically 5-year survival rates have been in the range of 10 to 20%.[4; 5; 6] Patients with metastatic disease are often symptomatic with a consequent low quality of life and marked decrements in physical and mental functioning.[7; 8] An activating mutation of the BRAF gene in the mitogen-activated protein kinase (MAPK) pathway which plays a critical role in regulating melanocyte growth, differentiation and survival, has been identified as driving the development of approximately 45-50% of melanomas.[9] The presence of the BRAF V600 mutation has been associated with an increased risk of mortality and shortened survival time compared with having BRAF wild-type disease.[10; 11]

Treatment pathway

The introduction of the BRAF inhibitors, dabrafenib and vemurafenib, which inhibit the enzymatic activity of the mutated BRAF protein, marked a step change in the management of BRAF V600 mutation-positive melanoma. Their use in monotherapy now represents the current UK standard of care for the first-line systemic treatment of patients with unresectable (stage IIIc) or metastatic (stage IV) disease. UK market research data confirms that the majority of patients (>70%) with BRAF mutation-positive metastatic melanoma receive first-line therapy with a single-agent BRAF inhibitor and only a small proportion (<5%) receive ipilimumab[a].[12; 13]

Although dabrafenib and vemurafenib significantly increase response rates and progression-free survival (PFS) compared with dacarbazine[14; 15], their efficacy as single-agents is limited by the emergence of intracellular resistance and disease progression can develop within 7 months of treatment initiation. Median survival times for patients receiving these BRAF inhibitor monotherapies are under 24 months[16; 15] and there remains a significant unmet need for life-extending treatments for patients with BRAF V600 mutation-positive metastatic melanoma.

Combining a MEK with a BRAF inhibitor to simultaneously inhibit the MAPK pathway downstream of BRAF via MEK 1/2 was identified as an approach to address the problem of resistance (see Section 2.1.1). Clinical studies confirm that substantial improvements in outcomes are delivered by the combination of trametinib + dabrafenib[b] over BRAF inhibitor monotherapy in this patient population[17; 18; 19; 20] (summarised in section 1.3 and discussed in more detail in section 4), such that it now offers a further treatment advancement for patients

[a] Remaining patients receive chemotherapy, best supportive care or are entered into a clinical trial.
[b] The combination of trametinib plus dabrafenib is referred to as trametinib + dabrafenib throughout this submission.

with BRAF V600 mutation-positive metastatic melanoma. The innovative nature of this combination was recognised by the U.S. Food and Drug Administration (FDA) who approved it in January 2014 through the FDA's Accelerated Approval program.

1.1 Statement of decision problem

The decision problem addressed in the submission is presented in Table 1 below.

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
Intervention	Trametinib in combination with dabrafenib	Trametinib in combination with dabrafenib	In line with final NICE scope
Population	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
Comparators	• Dabrafenib • Vemurafenib	• Dabrafenib monotherapy • Vemurafenib monotherapy	In line with final NICE scope
Outcomes	The outcome measures to be considered include: • progression free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life.	The outcome measures considered include: • progression free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life.	In line with final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	The economic analysis estimates pairwise and incremental cost-effectiveness of trametinib + dabrafenib combination versus dabrafenib monotherapy and vemurafenib, from the perspective of the NHS. DH agreed patient access schemes are taken into account in the PAS addendum. The model horizon is 30 years, approximating the patient's lifetime.	In line with final NICE scope.
Other consider-ations	If evidence allows, consideration should be given to trametinib in combination with dabrafenib as a first-line therapy or after treatment with immunotherapy. Guidance will only be issued in	The evidence presented in this submission relates almost entirely to the combined use of trametinib + dabrafenib as a first-line therapy in the population under consideration, consistent with the clinical evidence base for	In line with final NICE scope

	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.	this combination.	

1.2 Description of the technology being appraised

Details of the technology being appraised are summarised in Table 2 below. Novartis acquired the assets, dabrafenib and trametinib, from GlaxoSmithKline (GSK) in March 2015.

Table 2: Technology being appraised

UK approved names and brand names	Trametinib (Mekinist®) Dabrafenib (Tafinlar®)
Marketing authorisation	The combination of trametinib + dabrafenib received marketing authorisation on the 25th August 2015. Both agents are also licensed in monotherapy (Dabrafenib 26th August 2013; Trametinib 30th June 2014).
Indication	Trametinib in combination with dabrafenib (or dabrafenib in combination with trametinib) is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Confirmation of BRAF V600 mutation status using a validated test is required to select patients for treatment.
Method of administration	Trametinib and dabrafenib are both oral therapies. Trametinib is available in the UK as 0.5mg and 2mg film-coated tablets. Dabrafenib is available as 50mg and 75mg hard capsules. The recommended starting dose for combination therapy is: trametinib 2mg once daily *plus* dabrafenib 150mg (two x 75mg capsules) twice daily. Treatment with both drugs should be continued until disease progression or unacceptable toxicity. Management of adverse reactions may require dose reduction, treatment interruption or discontinuation according to the adverse event profiles of each medicine. See Table 6 for further information.
Mode of action	Dabrafenib is a selective inhibitor of BRAF V600 kinase activity. Trametinib is a selective inhibitor of MEK 1/2 which sits downstream of BRAF. Their use in combination provides concomitant inhibition of the MAPK signalling pathway by simultaneously targeting BRAF and MEK kinases.[21; 22] Pre-clinically the combination of trametinib + dabrafenib has shown greater inhibitory activity against BRAF-mutant cancer cells than either drug alone and to delay the emergence of resistance to BRAF inhibitor therapy.[23] Pre-clinical studies also demonstrate that the addition of trametinib to dabrafenib reduces the occurrence of hyperproliferative skin lesions originating from BRAF-inhibitor induced paradoxical activation of the MAPK pathway.[24]

1.3 Summary of the clinical effectiveness evidence

A systematic review identified three RCTs relevant to this appraisal: two Phase III RCTs comparing trametinib + dabrafenib with dabrafenib or vemurafenib as monotherapy (COMBI-d [MEK115306] versus dabrafenib[17; 18]; and COMBI-v (MEK116513] versus vemurafenib[19; 20]), plus a supportive Phase II study (BRF113220 [Part C] versus dabrafenib[25; 26]), together enrolling 1,289 patients with BRAF V600 mutation-positive metastatic melanoma.

From a clinical perspective, the comparative efficacy and safety evidence for trametinib + dabrafenib combination therapy versus the comparators comes directly from these head-to-head trials, with the large robust Phase III studies forming the primary evidence source. For the purposes of the economic evaluation, individual patient level time-to-event data (PFS and OS) have been pooled from the COMBI-d and COMBI-v studies on the basis of their trial designs and patient populations being near identical (discussed further in Section 4.9 and Appendix 8.13).

Efficacy

Key outcomes for the Phase III RCTs are summarised in Table 3 overleaf and discussed in further detail in Section 4.

Table 3: Primary & secondary efficacy endpoints in COMBI-d and COMBI-v (ITT populations)

		COMBI-d (MEK115306)[18] Latest cut-off: 12 January 2015		COMBI-v (MEK116513)[20] Latest cut-off: 13 March 2015	
		Trametinib + dabrafenib N=211	**Dabrafenib monotherapy N=212**	**Trametinib + dabrafenib N=352**	**Vemurafenib monotherapy N=352**
Median follow-up time, months		20.0	16.0	19.0	15.0
Progression-free survival (Primary endpoint in COMBI-d)	Median, months (95% CI)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	12.6 (10.7, 15.5)	7.3 (5.8, 7.8)
	HR (95% CI) p-value	0.67 (0.53, 0.84) p=0.0004		0.61 (0.51, 0.73) p<0.001	
Overall survival (Primary endpoint in COMBI-v)	Median, months (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	25.6 (22.6, NR)	18.0 (15.6, 20.7)
	HR (95% CI) p-value	0.71 (0.55, 0.92) p=0.011		0.66 (0.53, 0.81) p<0.001	
	1-year OS % (95% CI)	74% (67, 79)	68% (61, 74)	73% (68, 77)	64% (59, 69)
	2-year OS % (95% CI)	51% (44, 58)	42% (35, 49)	51% (45, 57)	38% (32, 44)
	% crossover	Not applicable		21 / 352 (6%)	
	RPSFTM-adjusted HR (95% CI)	Not applicable		0.63 (0.50, 0.79)	
Overall response rate	ORR (CR + PR), n (%) (95% CI)	144 (69%) (61.8, 74.8)	112 (53%) (46.3, 60.2)	231 (66%) (60.4, 70.6)	186 (53%) (47.5, 58.2)
	p-value	p=0.0014		p=0.0008	
Duration of response	Median, months (95% CI)	12.9 (9.4, 19.5)	10.6 (9.1, 13.8)	13.8 (11.2, 18.1)	8.5 (7.4, 9.7)

CR=complete response, PR=partial response, NR=not reached, RPSFTM=Rank Preserving Structural Failure Time Model

The combination of trametinib + dabrafenib demonstrated statistically significant reductions (of approximately 30%) in the risk of death compared with BRAF inhibitor monotherapy. Median overall survival (OS) for the combination was more than 25 months representing a clinically meaningful extension to survival of at least 6 months compared with dabrafenib (6.4 month median gain) or vemurafenib (7.6 month median gain) as monotherapy.[18; 20]

A small proportion (6%) of patients in the vemurafenib arm in COMBI-v switched to receive the combination after the study was stopped for efficacy following a planned interim analysis, which may have impacted the OS treatment effect. Adjustment for crossover using the accepted RPSFT methodology yielded an adjusted OS HR of 0.63 (95% CI: 0.50, 0.79) for the combination versus vemurafenib alone.[27] More than half of patients (51%) were still alive on combination therapy after 2 years compared with 38-42% on BRAF inhibitor monotherapy.[18; 20]

Across the Phase III studies there was a reduction in the risk of progression or death of at least 33%. Median progression-free survival (PFS) was significantly prolonged with trametinib + dabrafenib combination therapy and in the range of 11.0 to 12.6 months, compared with dabrafenib (8.8 months) or vemurafenib (7.3 months) monotherapy. Overall response rates (ORR) were significantly higher for combined trametinib + dabrafenib therapy (66-69% vs. 53%) compared with BRAF inhibitor monotherapy, and where responses occurred with the combination they lasted for more than a year (12.9 to 13.8 months).[18; 20]

Subgroup analyses indicated that the combination was more effective than BRAF inhibitor monotherapy, irrespective of BRAF mutation type, age, gender, performance status, LDH level, disease stage and other prognostic factors.[18; 19; 20]

Health-related quality of life (HRQoL)

Further, the efficacy superiority of the combination translates into statistically significant and clinically meaningful improvements in many aspects of health-related quality of life (HRQoL) (including overall health, functional, and symptomatic benefits particularly with respect to pain) for patients receiving the combination compared with single-agent BRAF inhibition.[28; 29] Thus, the adverse event (AE) profile associated with receiving the two drugs in combination does not negatively impact on patients' HRQoL.

Safety

The safety profile of trametinib + dabrafenib combination therapy generally reflects the known safety profile of the individual agents. Some AEs occur less frequently when the two drugs are co-administered than with single-agent BRAF inhibitors, whilst others are more prevalent.

The most common AEs for trametinib + dabrafenib combination therapy (occurring in ≥ 20% patients in the clinical studies) include: pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, and vomiting.[21; 22]

Pyrexia is the most notable AE associated with the combination and is increased in incidence versus dabrafenib monotherapy. However, ≤7% of patients experienced Grade 3 pyrexia in the clinical studies and there were no Grade 4 events. Most cases of pyrexia can be simply

managed with anti-pyretic medication and/or treatment interruption; ≤4% of pyrexia events led to permanent treatment discontinuation.[18; 19; 20]

The incidence of skin-related toxicities (e.g. hyperkeratosis, hand-foot syndrome, alopecia, skin papilloma, cutaneous squamous cell carcinoma [cuSCC]) associated with BRAF inhibitor therapy is reduced through the addition of trametinib to dabrafenib.[19; 20] Photosensitivity reactions (4% vs. 23%) and arthralgia (27% vs. 52%) were also less frequent with trametinib + dabrafenib combination therapy than with vemurafenib alone.[20] This attenuation in AEs may contribute to the positive perception of HRQoL by patients receiving the combination, given the physical, psychological and/or quality-of-life impact of some of these conditions.

Recognised class effects of MEK inhibitors were observed with trametinib + dabrafenib including: dermatitis acneiform (≤10%); decrease in ejection fraction (≤8%); chorioretinopathy (≤1%). Other AEs of special interest were infrequent and included: cuSCC (including keratoacanthoma) (≤3%); non-cutaneous malignancies (1%); and new primary melanoma (<1%).[18; 19; 20]

Approximately half of all the AEs experienced by patients on combination treatment in the Phase III trials were Grades 1 and 2; the rates of Grade 3/4 events were slightly lower in the combination than in the monotherapy arms. Discontinuation rates due to AEs were 9-16% across all the trials indicating that the majority of patients could stay on combination therapy, with their AEs being managed through dose reductions/interruptions.[18; 20; 30]

Overall, trametinib + dabrafenib combination therapy has a safety profile that is manageable with appropriate interventions and monitoring as recommended on the SPCs.

1.4 Summary of the cost-effectiveness analysis

Pairwise and incremental cost effectiveness of trametinib + dabrafenib versus dabrafenib and vemurafenib monotherapies was assessed, from the NHS perspective, in a three state partitioned survival model (PFS, post-progression survival [PPS] and death) with a 30-year time horizon. Pooled data from COMBI-v and COMBI-d underpinned the assessment and given that the proportional hazards assumption does not hold in the dataset, the individual arms were treated independently. For PFS and OS, Kaplan Meier data were used until a particular time point beyond which there appeared to be long-term linear trends in each of the hazard functions. For PFS a constant hazard (as determined at the break point) was assumed thereafter in each arm for the duration of the projection. For OS, constant hazards were assumed from the break point until year 5 at which it was assumed the hazard trends would follow those of case-mix adjusted AJCC survival. Beyond 20 years general population mortality trends were applied accounted for the residual increased mortality rate in this population. This approach to OS has high face validity and results in projections which are consistent with a body of literature on long-term survival in patients with metastatic melanoma.

Health states were valued using EQ-5D utilities collected directly from patients in COMBI-v and COMBI-d. Outcomes were measured in terms of quality adjusted life years (QALYs). The incremental cost components were treatment acquisition costs, drug dispensing costs,

pre- and post-progression monitoring/ supportive care costs, costs of treating adverse events and the costs of post-study anti-cancer therapies. Patient access schemes apply to the intervention and comparators in this appraisal and they are accounted for in the PAS addendum and in the overall conclusions.

Base case pairwise and incremental results using the list prices are presented in Table 4 and Table 5. At list price, the trametinib + dabrafenib combination is not cost-effective versus either dabrafenib or vemurafenib. When PAS are applied the combination of trametinib + dabrafenib is a cost effective alternative to dabrafenib and vemurafenib monotherapies (as shown in the confidential PAS addendum). At list prices, probabilistic sensitivity analyses for the base case suggest that at a threshold of £50,000/QALY, trametinib + dabrafenib would not be cost-effective versus vemurafenib or dabrafenib (0% of cases). The picture changes considerably when patient access schemes are incorporated (see PAS addendum).

Table 4: Pairwise cost-effectiveness results (all treatments at list prices)

	Trametinib+ dabrafenib	Vemurafenib	Dabrafenib
Technology acquisition cost	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Difference in total costs	N/A	129,275	134,802
LYG	4.586	2.933	2.933
LYG difference	N/A	1.653	1.653
QALYs	3.443	2.098	2.146
QALY difference	N/A	1.345	1.298
ICER	N/A	96,437	104,069
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio			

Table 5: Incremental cost-effectiveness results (all treatments at list prices)

Technology (and comparators)	Total cost	Total QALY	Incremental cost	Incremental QALY	ICERs versus baseline	Incremental analysis
Dabrafenib	[redacted]	2.146	-	-	-	-
Vemurafenib	[redacted]	2.098	5,351	-0.047	dominated	dominated
Trametinib+ dabrafenib combination	[redacted]	3.443	129,707	1.345	104,069	104,069

1.5 Summary

Large head-to-head studies clearly demonstrate the substantial efficacy benefits provided by trametinib + dabrafenib combination therapy in prolonging PFS, achieving high response rates, and extending survival, compared with dabrafenib or vemurafenib as monotherapy. This translates into meaningful improvements in HRQoL for patients receiving the combination, with a safety profile that is manageable and results in a reduction in incidence of some AEs versus single-agent BRAF inhibitor therapy.

Trametinib + dabrafenib combination therapy delivers a median extension to life of at least 6 months compared with BRAF inhibitor monotherapy, the current standard of care which carries a life expectancy of less than 24 months (see Section 4.13.3), and thus the combination meets the criteria for an end-of-life treatment given the small patient population involved (<1000 patients).

A robust cost-effectiveness analysis utilising pooled time-to-event data from the highly comparable phase III head-to-head trials results in ICERs below £50,000/QALY for trametinib + dabrafenib versus both dabrafenib and vemurafenib monotherapies, when patient access schemes are incorporated.

Novartis Pharmaceuticals UK Limited is therefore seeking a positive recommendation for the combination of trametinib + dabrafenib as a clinically superior and cost-effective alternative to BRAF inhibitor monotherapy for all adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, consistent with its licensed indication.

All cost-effectiveness estimates incorporate the treatment and comparators at list prices (due to existing *confidential* PAS which are in place), and are therefore not reflective of the actual cost to the NHS. The confidential PAS addendum presents results incorporating the actual or estimated drug acquisition costs incorporating the discounts.

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. For devices, provide details of any different versions of the same device.

Generic name	Trametinib (dimethyl sulphoxide)	Dabrafenib (mesilate)
Brand name	Mekinist ®	Tafinlar ®
UK approved name	Mekinist 0.5mg, 1mg* and 2mg film-coated tablets	Tafinlar 50mg and 75mg hard capsules
Therapeutic class	Antineoplastic agents – Protein kinase inhibitor.	Antineoplastic agents – Protein kinase inhibitor.

* 1mg strength not commercially available in UK

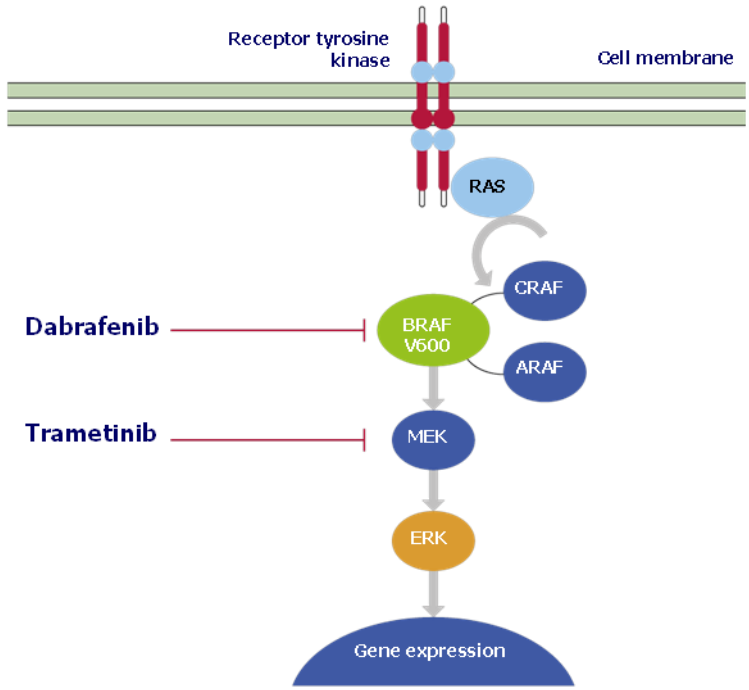
Note: Both drugs are also licensed as monotherapy. There has been no reformulation or repackaging of the drugs specifically for their use in combination.

<u>Mechanism of action:</u>

The mitogen-activated protein kinase (MAPK) signalling pathway plays a key role in regulating the growth, proliferation and survival of normal cells, including melanocytes.[31; 32] A mutation of the BRAF protein on the MAPK pathway, resulting in constitutive activation of the pathway, has been identified as driving the development of approximately 45-50% of melanomas.[9; 10]

Dabrafenib is an orally bioavailable and selective inhibitor of BRAF V600 kinase activity.[21] Trametinib is an orally bioavailable and selective inhibitor of MEK1 and MEK2 [22], additional key components of the MAPK pathway which sit downstream of BRAF (see Figure 1). Thus, the combination of trametinib + dabrafenib provides concomitant inhibition of the MAPK pathway by simultaneously targeting two discrete kinases.[21; 22]

Figure 1: Schematic of MAPK signalling pathway showing where dabrafenib and trametinib act



Despite the encouraging response rates seen in clinical trials, disease progression can develop within 7 months when BRAF inhibitors are used as monotherapy [14; 15] (the current standard of care for BRAF-mutation positive metastatic melanoma), indicating the development of intracellular resistance to treatment.

Several resistance mechanisms have been identified, including ones that lead to re-activation of the MAPK pathway.[25; 33; 34] Recognition of these mechanisms led to the hypothesis that inhibiting the cellular pathway downstream of BRAF, through MEK 1/2, may at least delay the emergence of resistance.[25] This subsequently provided the rationale for investigating the addition of trametinib to dabrafenib as a treatment option in this patient group.

Pre-clinically the combination of trametinib + dabrafenib has been shown to block rebound pERK signalling and produce more potent anti-tumour activity in BRAF V600 melanoma cell lines than either drug alone. Used together the drugs prolong inhibition of tumour growth and delay the emergence of resistance to BRAF inhibitor therapy in BRAF V600 mutation-positive melanoma xenografts.[23; 35; 36]

The emergence of hyperproliferative lesions, such as cutaneous squamous cell carcinomas (cuSCCs), early in the course of BRAF inhibitor therapy has been linked to a paradoxical activation of the MAPK pathway.[25] In an experimental model of cuSCC, the addition of a MEK inhibitor to a BRAF inhibitor was found to reduce this effect [24], likely due to attenuation of BRAF-inhibitor induced MAPK signalling by the MEK inhibitor.[25]

Results of large randomised clinical studies now support the mechanistic hypothesis and preclinical work to demonstrate that combined trametinib + dabrafenib therapy leads to a substantial increase in efficacy over BRAF inhibitor monotherapy.[18; 20] Additionally, cutaneous adverse events related to paradoxical MAPK pathway activation manifest in

patients less frequently when trametinib + dabrafenib is co-administered, than when BRAF inhibitors are used alone.[18; 19]

2.2. Marketing authorisation/CE marking and health technology assessment

2.2.1. Indicate whether the technology has a UK marketing authorisation/CE marking for the indications detailed in this submission. If so, give the date on which this was received. If not, state the current UK regulatory status, with relevant dates (for example, date of application and/or expected date of approval from the Committee for Human Medicinal Products).

The combination of trametinib + dabrafenib was granted marketing authorisation by the European Medicines Agency (EMA) on the 25th August 2015 for use in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Both agents are also licensed for use as monotherapies in the same patient population. Dabrafenib was first licensed as a monotherapy on 26th August 2013. Trametinib received a monotherapy licence on 30th June 2014.

2.2.2. Give the (anticipated) indication(s) in the UK. For devices, provide the date of (anticipated) CE marking, including the indication for use. If a submission is based on the company's proposed or anticipated marketing authorisation, the company must advise NICE immediately of any variation between the anticipated and the final marketing authorisation approved by the regulatory authorities.

The combination of trametinib + dabrafenib is already licensed for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma (see 2.2.1). The combination indication for the respective components is as follows:

"Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation".[22]

"Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation".[21]

2.2.3. Summarise any (anticipated) restrictions or contraindications that are likely to be included in the (draft) summary of product characteristics (SmPC).

Trametinib + dabrafenib combination treatment is contra-indicated in anyone who is hypersensitive to trametinib or any of the excipients in trametinib tablets[22], or anyone who is hypersensitive to dabrafenib or any of the excipients in dabrafenib capsules.[21]

Special Warnings & Precautions for the combined use of trametinib + dabrafenib include (listed alphabetically): Deep vein thrombosis/Pulmonary embolism; Haemorrhage; Hepatic events/Hepatic impairment; Hypertension; Interstitial lung disease /pneumonitis; Left

ventricular ejection fraction reduction/left ventricular dysfunction; New malignancies (Cutaneous squamous cell carcinoma; New primary melanoma; RAS-associated non-cutaneous secondary/recurrent malignancy); Pancreatitis; Pyrexia; Rash; Renal failure; Rhabdomyolysis; QT prolongation; Visual impairment (Uveitis; Retinal vein occlusion; Retinal pigment epithelial detachment). Further details can be found in the Summary of Product Characteristics (SPCs) for both dabrafenib and trametinib provided in the reference pack accompanying this submission.

2.2.4. Include the (draft) SmPC for pharmaceuticals or information for use (IFU) for devices in an appendix.

The SPCs for dabrafenib and trametinib are provided in the reference pack accompanying this submission.

2.2.5. Provide the (draft) assessment report produced by the regulatory authorities (that is, the European public assessment report for pharmaceuticals) and a (draft) technical manual for devices in an appendix.

The European Public Assessment Report (EPAR) pertaining to the licence variation for the use of trametinib in combination with dabrafenib can be found in in the reference pack accompanying this submission.

2.2.6. Summarise the main issues discussed by the regulatory authorities (preferably by referring to the [draft] assessment report [for example, the European public assessment report]). State any special conditions attached to the marketing authorisation (for example, if it is a conditional marketing authorisation).

As discussed in the EPAR, the regulatory authorities raised a concern regarding the combined use of trametinib + dabrafenib as a second-line therapy in patients who had already progressed on single-agent BRAF inhibitor therapy.[37] In the Phase II BRF113220 study, overall responses with the combination were seen in a limited number (<15%) of patients who had experienced progression on previous BRAF inhibitor therapy (n=4/26 patients in Part B, and n=6/45 patients who crossed over in Part C).[38] Because of the lack of robust data in patients that have progressed on BRAF inhibitor therapy, a warning was included in the SPCs to highlight the limited data for the combination in this particular patient population (see trametinib and dabrafenib SPCs sections 4.4 and 5.1).[21; 22]

Another concern lay with the limited data for the combination in patients with brain metastases.[37] Due to the strict inclusion and exclusion criteria of the studies, fewer than 20 patients with a history of brain metastases were treated in the clinical trials. Therefore, the efficacy of combination therapy for patients with a history of brain metastasis is not known at present and a statement was included in the SPCs (see sections 4.4 and 5.1) to inform prescribers of the limited data in this patient population. A Phase II study is currently ongoing

to evaluate the effect of trametinib + dabrafenib combination therapy in patients with BRAF V600 mutation-positive melanoma that is metastatic to the brain (BRF117277; NCT02039947).

There are no special conditions attached to the marketing authorisation for the combination of trametinib + dabrafenib (nor their use as monotherapies).

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

Dabrafenib was made commercially available in the UK on 1st January 2014, following marketing authorisation for its use as a monotherapy on 26th August 2013.

Trametinib (and therefore trametinib + dabrafenib combination therapy) was made commercially available in the UK during November 2015.

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

The European Commission approval for trametinib + dabrafenib combination therapy applies to all 28 EU member states, plus Iceland, Norway and Liechtenstein.

The combination of trametinib + dabrafenib for patients with unresectable or metastatic melanoma who have BRAF V600 mutation is also approved in the following countries:

Country	Approval date
US	8/9th January 2014
Australia	11th February 2014
Chile	22nd September 2014
Canada	6th March 2015
New Zealand	26th March 2015

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.

Novartis Pharmaceuticals UK Limited expects to make a submission for trametinib + dabrafenib combination therapy in BRAF V600 mutation-positive unresectable/metastatic melanoma to the Scottish Medicines Consortium (SMC) during Q1 2015.

2.3. Administration and costs of the technology

2.3.1. For pharmaceuticals, complete the table 'Costs of the technology being appraised' including details of the treatment regimen and method of administration. Indicate whether the acquisition cost is list price or includes a patient access scheme, and the anticipated care setting. Specify the sources of information and data used to complete the table, for example SmPC or trial data. For more information see section 5.5 of the NICE guide to the methods of technology appraisal.

Table 6: Administration and costs of the technology

	Trametinib	Dabrafenib	Data sources
Pharmaceutical formulation	Film-coated tablets; (Modified oval, yellow 0.5mg; Round, pink 2mg)	Hard capsules (Opaque dark red 50mg; Opaque dark pink 75mg)	Trametinib SPC Dabrafenib SPC
Method of administration	Oral. Tablets to be taken with a full glass of water; not to be chewed or crushed and taken at least 1 hour before or 2 hours after a meal; take at a similar time every day, either with morning or evening dose of dabrafenib.	Oral. Capsules should be swallowed whole with water; not be chewed or crushed and taken at least 1 hour before or 2 hours after a meal; leave an interval of ~12 hours between doses and take at similar times each day (morning and evening).	Trametinib SPC Dabrafenib SPC
Doses	Recommended starting dose: 2mg once daily (in combination with dabrafenib 150mg twice daily).	Recommended starting dose: 150mg (two x 75m capsules) twice daily (in combination with trametinib 2mg once daily). Total daily dabrafenib dose = 300mg.	Trametinib SPC Dabrafenib SPC
Dosing frequency	Once daily	Twice daily	
Acquisition cost (excluding VAT)	NHS list price trametinib: 28 day supply = £4,480.00 (30 x 2mg: £4,800 | 7 x 2mg £1,120 | 30 x 0.5mg £1,200 | 7 x 0.5mg £280) Proposed price incorporating the confidential PAS is listed in the PAS addendum.	NHS list price dabrafenib: 28 day supply = £5,600 (28 x 75mg: £1,400 | 28 x 50mg: £933.33) Proposed price incorporating the confidential PAS is listed in the PAS addendum.	BNF (October 2015)
Median length of a course of treatment	Taken continuously until the patient no longer derives benefit or the development of unacceptable toxicity. Median PFS for the trametinib + dabrafenib combination arm was 11.0 months in the COMBI-d trial[18], and 12.6 months in the COMBI-v trial[20].	Taken continuously until the patient no longer derives benefit or the development of unacceptable toxicity. Median PFS for the trametinib + dabrafenib combination arm was 11.0 months in the COMBI-d trial[18], and 12.6 months in the COMBI-v trial[20].	COMBI-v (Robert *et al*., 2015) and COMBI-d (Long *et al*., 2015) clinical trials
Median cost of a course of treatment	Trametinib + dabrafenib combination therapy: At list price, the median cost of a course of treatment is £129,210.* *(£10,080 x ([365/12]/28) x 11.8 = £129,210)		Based on an assumed median PFS for combination of 11.8 months (as above).
Anticipated average interval between courses of	N/A. One course per patient, taken continuously until the patient no longer derives benefit or the development of unacceptable toxicity	As with trametinib	Trametinib SPC Dabrafenib SPC

<table>
<tr><td>treatments</td><td></td><td></td><td></td></tr>
<tr><td>Anticipated number of repeat courses of treatments</td><td>Repeat courses are not anticipated; patients are treated until they no longer derive benefit or develop unacceptable toxicity.</td><td>As with trametinib</td><td>Trametinib SPC
Dabrafenib SPC</td></tr>
<tr><td>Dose adjustments</td><td>Management of adverse reactions may require dose reduction, treatment interruption or discontinuation.

Recommended trametinib dose level reductions
<table>
<tr><th>Dose Level</th><th>Dose/Schedule</th></tr>
<tr><td>Full dose</td><td>2 mg o.d.</td></tr>
<tr><td>First reduction</td><td>1.5 mg o.d.</td></tr>
<tr><td>Second reduction</td><td>1 mg o.d.</td></tr>
<tr><td>Third reduction</td><td>1 mg o.d.</td></tr>
</table>
Dose adjustment for trametinib below 1 mg o.d. is not recommended.

Trametinib dose modification schedule based on the grade of any AEs
<table>
<tr><th>Grade (CTC-AE)*</th><th>Recommended trametinib dose modifications</th></tr>
<tr><td>Grade 1 or Grade 2 (Tolerable)</td><td>Continue treatment and monitor as clinically indicated</td></tr>
<tr><td>Grade 2 (Intolerable) or Grade 3</td><td>Interrupt therapy until toxicity is grade 0-1 and reduce by one dose level when resuming therapy</td></tr>
<tr><td>Grade 4</td><td>Discontinue permanently, or interrupt therapy until grade 0-1 and reduce by one dose level when resuming therapy</td></tr>
</table>
* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0</td><td>Management of adverse reactions may require dose reduction, treatment interruption or discontinuation.

Recommended dabrafenib dose level reductions
<table>
<tr><th>Dose Level</th><th>Dose/Schedule</th></tr>
<tr><td>Full dose</td><td>150 mg b.d.</td></tr>
<tr><td>First reduction</td><td>100 mg b.d.</td></tr>
<tr><td>Second reduction</td><td>75 mg b.d.</td></tr>
<tr><td>Third reduction</td><td>50 mg b.d.</td></tr>
</table>
Dose adjustment for dabrafenib below 50 mg b.d. is not recommended.

Dabrafenib dose modification schedule based on the grade of any AEs
<table>
<tr><th>Grade (CTC-AE)*</th><th>Recommended dabrafenib dose modifications</th></tr>
<tr><td>Grade 1 or Grade 2 (Tolerable)</td><td>Continue treatment and monitor as clinically indicated</td></tr>
<tr><td>Grade 2 (Intolerable) or Grade 3</td><td>Interrupt therapy until toxicity is grade 0-1 and reduce by one dose level when resuming therapy</td></tr>
<tr><td>Grade 4</td><td>Discontinue permanently, or interrupt therapy until grade 0-1 and reduce by one dose level when resuming therapy</td></tr>
</table>
* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0</td><td>Trametinib SPC
Dabrafenib SPC</td></tr>
</table>

	When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. Trametinib dose should not exceed 2mg once daily. If treatment-related toxicities occur during trametinib + dabrafenib combination therapy, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only trametinib are: left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO); retinal pigment epithelial detachment (RPED); interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib). Further details are provided in the trametinib SPC relating to management of specific AEs.	When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. Dabrafenib dose should not exceed 150mg twice daily. If treatment-related toxicities occur during trametinib + dabrafenib combination therapy, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only dabrafenib are: pyrexia; uveitis; RAS mutation-positive non cutaneous malignancies; QT prolongation (primarily related to dabrafenib). Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma. Dabrafenib should be interrupted if patient's temperature is ≥38.5^{o}C. Patients should be evaluated for signs and symptoms of infection. Further details are provided in the dabrafenib SPC relating to management of specific AEs.	
Anticipated care setting	Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products. Trametinib is an oral tablet therapy and therefore can be administered by the patient or their carer at home. Whilst not explicitly stated on the SPC, it is expected that patients will attend monthly out-patient visits in a hospital setting for ongoing review and monitoring.	Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products. Dabrafenib is an oral capsule therapy and therefore can be administered by the patient or their carer at home. Whilst not explicitly stated on the SPC, it is expected that patients will attend monthly out-patient visits in a hospital setting for ongoing review and monitoring.	Trametinib SPC Dabrafenib SPC

2.3.2. Provide details of any patient access scheme that has been referred to NICE for inclusion in the technology appraisal by ministers and formally agreed by the company with the Department of Health before the date of evidence submission to NICE for the technology. For more information see section 5 of the NICE guide to the processes of technology appraisal.

Novartis Pharmaceuticals UK Limited has submitted an application to PASLU for a simple discount scheme for trametinib.

There is already a confidential discount scheme in place for dabrafenib which became effective on 1st October 2014.

For the purposes of the cost-effectiveness analyses supporting this submission, these discounts are applied in the PAS addendum. All analyses presented in the main submission document are based on list prices.

2.3.3. For devices, provide the list price and average selling price in a table similar to the table presented in the template, 'Costs of the technology being appraised'. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

2.4. Changes in service provision and management

2.4.1. State whether additional tests or investigations are needed (for example, diagnostic tests to identify the population for whom the technology is indicated in the marketing authorisation) or whether there are particular administration requirements for the technology. For more information see section 5.9 of the NICE guide to the methods of technology appraisal.

Dabrafenib and trametinib are both targeted therapies for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. BRAF V600 mutations are found in approximately 45-50% of melanomas.[9; 10] Before taking the combination of trametinib + dabrafenib, patients must have confirmation of BRAF V600 mutation status using a validated test.

Since the introduction of the BRAF inhibitors (vemurafenib and dabrafenib) for use in monotherapy, BRAF testing has become part of routine clinical care for patients with unresectable or metastatic melanoma and there is now England-wide availability of BRAF testing facilities. Indeed, the recently published NICE guideline for melanoma specifies that genetic testing should be offered to patients if a targeted systemic therapy is a possible treatment option.[39] For these reasons, the cost of BRAF testing is not incorporated into the economic evaluation being undertaken in this appraisal. In any case, the costs would be equivalent across intervention and comparator arms. It is therefore unlikely that there will be

any additional burden on NHS pathology services following the availability of trametinib + dabrafenib combination therapy.

As discussed in section 2.4.4, the nature of the tests and monitoring required for patients on trametinib + dabrafenib combination therapy are very similar to those required for patients receiving single-agent BRAF inhibitors, the current standard treatment for patients with BRAF V600 mutation-positive metastatic melanoma. The only additional monitoring requirement relates to evaluation of left ventricular ejection fraction (LVEF) which the SPC recommends prior to initiation of trametinib + dabrafenib, after 1 month, and then at approximately 3-monthly intervals, driven by the introduction of the MEK inhibitor component.[22]

There are no special administration requirements for the technology, and as an all-oral therapy, trametinib + dabrafenib can be administered simply by patients or their carers at home.

2.4.2. Identify the main resource use to the NHS associated with the technology being appraised. Describe the location or setting of care (that is, primary and/or secondary care, commissioned by NHS England specialised services and/or clinical commissioning groups), staff costs, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Table 7 summarises the main resource use to the NHS associated with trametinib + dabrafenib combination treatment compared with the current use of BRAF inhibitor monotherapy.

Table 7: Main resource use associated with the technology versus the comparators

	Trametinib + dabrafenib combination therapy	BRAF inhibitor monotherapy	Data sources
Location/ setting of care	Hospital out-patient visits for initiation of therapy, and follow-up. Treatment can be administered at home.	Hospital out-patient visits for initiation of therapy, and follow-up. Treatment can be administered at home.	Not applicable.
Admin-istration costs	As oral therapies, there are no administration costs associated with trametinib + dabrafenib. There is a small requirement for a hospital pharmacists' time to dispense packs (see Section 5.5).	As an oral therapy, there are no administration costs associated with BRAF inhibitor monotherapy. There is a small requirement for a hospital pharmacists' time to dispense packs (see Section 5.5).	See Section 5.5 for further information.
Staff costs	GP and specialist staff costs as required to dispense treatment, monitor the patient and address any AEs; see Section 5.5 for further details of costs	GP and specialist staff costs as required to dispense treatment, monitor the patient and address any AEs; see Section 5.5 for further details of costs	See Section 5.5 for further information.

	incorporated in the economic model.	incorporated in the economic model.	
Monitoring and tests	• Test to confirm tumour BRAF V600 mutation status • Regular skin examinations (prior to initiation of treatment, monthly during treatment, and for 6 months after discontinuation of treatment) to check for the development of cutaneous squamous cell carcinomas (CuSCCs) and other skin-related toxicities. • Patients should be monitored for ophthalmological problems while on therapy. This may involve questioning patients at routine clinic visits regarding any visual changes or visual symptoms and referring to ophthalmology to confirm diagnoses and assist with management if required. • Liver function tests (LFTs) should be carried out monthly during treatment. • Serum creatinine should be routinely monitored while on treatment. • ECG and electrolytes should be monitored before starting treatment, after one month, and after dose modification; further monitoring is recommended, particularly in patients with moderate to severe hepatic impairment. • Additional monitoring of patients for RAS-associated non-cutaneous malignancies may include blood	• Test to confirm tumour BRAF V600 mutation status • Regular skin examinations (prior to initiation of treatment, monthly during treatment, and for 6 months after discontinuation of treatment) to check for the development of cutaneous squamous cell carcinomas (CuSCCs) and other skin-related toxicities. • Patients should be monitored for ophthalmological problems while on therapy. This may involve questioning patients at routine clinic visits regarding any visual changes or visual symptoms and referring to ophthalmology to confirm diagnoses and assist with management if required. • Liver function tests (LFTs) should be carried out monthly during treatment. • Serum creatinine should be routinely monitored while on treatment. • ECG and electrolytes should be monitored before starting treatment, after one month, and after dose modification; further monitoring is recommended, particularly in patients with moderate to severe hepatic impairment. • Additional monitoring of patients for RAS-associated non-cutaneous malignancies may include blood	Trametinib SPC Dabrafenib SPC Vemurafenib SPC

	counts, head & neck examinations, chest/abdomen CT scans, and pelvic/anal examinations. • Evaluation of left ventricular ejection fraction (LVEF) prior to initiation of treatment, after 1 month, and then at approximately 3 monthly intervals.	counts, head & neck examinations, chest/abdomen CT scans, and pelvic/anal examinations.	

Note: This table does not reflect how costs have been incorporated in the economic model which is based on the MELODY study (Lorigan et al, 2014).

Treatment with trametinib + dabrafenib will be initiated by a secondary care physician experienced in the use of anti-cancer medicinal products, and patients will be supervised by healthcare professionals in a hospital out-patient setting. Dabrafenib and trametinib are both oral therapies and can be administered by the patient or their carer at home.

Before initiation of trametinib + dabrafenib therapy, patients must have confirmation of a BRAF V600 mutation using a validated test. This requires pathology services to test for the BRAF mutation on tumour excision or biopsy samples. As discussed in section 2.4.1 above, the resource associated with BRAF testing will be the same as it is currently.

There will only be limited impact on pharmacy resource through the introduction of trametinib for use in combination with dabrafenib. Our economic model assumes a dispensing cost of £13.60 for each prescription (based on the cost of 12 minutes of hospital pharmacist time). It is assumed that a 28-day supply of both dabrafenib and trametinib is prescribed every 4 weeks (28 days). Dabrafenib is available in 7-day packs; trametinib is available in 7-day and 30-day packs (the price per tablet is the same irrespective of the pack size dispensed).

Trametinib + dabrafenib combination therapy should be administered until disease progression or unacceptable toxicity. The main resource use to the NHS associated with trametinib + dabrafenib therapy is therefore expected to be related to the management of patients in the pre-progression period, as is the case with the BRAF inhibitor monotherapies.

The use of trametinib + dabrafenib combination therapy can infrequently incur ophthalmological reactions and cardiac complications[18; 20], and thus, other disciplines may occasionally need to be involved in order to review patients and assist with managing such conditions. The combination of trametinib + dabrafenib significantly improves PFS compared with BRAF inhibitor monotherapy (see section 4.7) which may increase resource use compared with the current standard of care, due to the longer period over which patients will need to be managed, though the nature of the resource use will be largely similar and there is unlikely to be a significant impact on existing services.

Resource requirements related to the management of adverse events (AEs) may vary slightly due to differences in the incidences of certain AEs associated with the combined use of trametinib + dabrafenib, compared with dabrafenib or vemurafenib as single agents. For example, the incidence of cutaneous AEs associated with BRAF inhibitor therapy is attenuated by the addition of trametinib to dabrafenib; thus, for example, the costs and

resources associated with surgeries to remove cuSCCs might be reduced. Conversely, the rate of pyrexia and associated use of anti-pyretic medications is likely to be increased through using trametinib in combination with dabrafenib compared with BRAF inhibitor monotherapy (however, most cases are mild to moderate and do not require hospitalisation).

The comparative AE profiles of trametinib + dabrafenib combination therapy versus dabrafenib or vemurafenib alone are discussed further in section 4.12.

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

The combination of trametinib + dabrafenib is not anticipated to require any additional infrastructure in the NHS to be put in place.

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

The patient monitoring required to support the combined use of trametinib + dabrafenib for BRAF V600 mutation-positive metastatic melanoma is unlikely to be significantly different to the clinical practice associated with the use of BRAF inhibitors as monotherapy, the current standard of care in this patient population.

Patients receiving active treatment for metastatic melanoma are clinically assessed for treatment effectiveness and monitored for adverse events during the course of their treatment. This is expected to be done on a monthly basis irrespective of the actual drug(s) being taken / administered.

Patients receiving trametinib + dabrafenib therapy require regular blood counts, and monitoring of blood pressure, renal and liver function. This would form part of routine clinical care for any patient receiving a BRAF inhibitor or most systemic treatments for advanced cancer.

Patients receiving BRAF inhibitor therapy already require regular monitoring for: the development of cuSCCs and other skin lesions and dermatological reactions; the occurrence of non-cutaneous malignancies; ophthalmological problems; and cardiac complications.[21; 40] The nature and frequency of the monitoring requirements for trametinib + dabrafenib combination therapy are therefore very similar to those for BRAF inhibitor monotherapy. The main difference in the monitoring required for trametinib + dabrafenib compared with single-agent BRAF inhibitors is likely to relate to the duration for which the majority of patients will require scans and need to be monitored for, driven by the longer PFS achieved with combination therapy versus dabrafenib or vemurafenib alone.

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.

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

2.5. Innovation

2.5.1. If you consider the technology to be innovative with potential to make a substantial impact on health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation:

- **state whether and how the technology is a 'step-change' in the management of the condition**
- **provide a rationale to support innovation, identifying and presenting the data you have used.**

The introduction of BRAF inhibitors has transformed the treatment landscape and outlook for patients with BRAF mutation-positive metastatic melanoma. Monotherapy with dabrafenib or vemurafenib has shown significant improvements in PFS and response rates compared with conventional chemotherapy (dacarbazine).[14; 15] However, BRAF inhibitors frequently give rise to problematic cutaneous toxicities through paradoxical activation of the MAPK pathway, and resistance develops through reactivation of the pathway resulting in a median PFS of about 7 months.[14; 15]

The scientific understanding of the underlying resistance mechanisms led to the rapid development (within 4 years) of trametinib, the first licensed MEK inhibitor. Single-agent trametinib has also demonstrated significant increments in PFS and OS compared with chemotherapy in the same patient group, and it is not associated with paradoxical activation of the MAPK pathway.[41]

Combining trametinib with dabrafenib optimises the utility, and addresses the limitations, of single-agent targeted therapy to provide a further step-change in treatment for this patient population. Their use in combination exploits their activity at discrete components within the important MAPK intracellular signalling pathway to provide more complete inhibition than either drug alone.[21; 22] This mechanistic rationale predicts for improved clinical outcomes; indeed, large clinical studies confirm that substantial efficacy gains (higher ORRs, more durable responses, prolonged PFS and OS) are obtained through using trametinib in combination with dabrafenib compared with a BRAF inhibitor alone.[17; 18; 19; 20]

Although the combination of two drugs potentially exposes patients to more AEs that might interfere with their lives, the health-related quality of life (HRQoL) findings demonstrate that combination therapy does not result in deterioration of patient-perceived HRQoL. In fact, the combination has shown statistically significant and clinically meaningful improvements over BRAF inhibitor monotherapy in many aspects of HRQoL (including overall health, functional and symptom dimensions) during study treatment and up to the disease progression visit.[28;

[29] It is possible that any HRQoL benefits experienced by patients in the post-progression period may be underestimated in our QALY[42] because the last HRQoL assessment in the COMBI-d and COMBI-v studies was made 5 weeks after progression.

Furthermore, the addition of trametinib to dabrafenib attenuates the incidence and severity of a number of the skin toxicities associated with BRAF inhibitor therapy (including hyperkeratosis, hand-foot syndrome, alopecia, and more serious cuSCCs and new primary melanomas).[17; 18; 19; 20] From a patient's point of view, the amelioration in some of these AEs might not be captured in the QALY calculation since the EQ-5D may be insufficiently sensitive in dermatological conditions, particularly those that impact on HRQoL.[43; 44] For example, Grade 1/2 alopecia involves up to 100% hair loss[c45], and whilst not physically harmful, can have a serious psychological impact[46]. Grade 2 hand-foot syndrome carries unpleasant skin changes (e.g. blisters, hyperkeratosis, bleeding, oedema) that can be painful and limit simple everyday tasks.[47] Similarly, even low grade photosensitivity can significantly interfere with daily activities and affect quality of life.[48; 49]

In summary from a patient's perspective, treatment with the combination of trametinib + dabrafenib provides a clear benefit over BRAF inhibitor monotherapy by integrating a significant extension to survival with a reduction in certain unpleasant side effects and uncomfortable disease-associated symptoms together with meaningful improvements in HRQoL. During the time when their disease is stable and/or under control, patients will be able to spend quality time with their family and friends, and may be able to participate in activities, and in some cases, return to or continue to work, and/or to contribute to society in other ways. This may be particularly the case given the younger population of patients who develop melanoma compared with other cancers.[3] Thus, there may be several elements of health-related benefit from trametinib + dabrafenib combination therapy that will not be adequately quantified in the estimates of QALY gain for this intervention versus the comparators.

The combination of trametinib + dabrafenib therefore provides a rational and innovative therapeutic strategy for patients with BRAF V600 mutation-positive metastatic melanoma. The innovative nature of the combination was recognised by the U.S. Food and Drug Administration (FDA) who approved it in January 2014 through the FDA's Accelerated Approval program contingent on the results of the COMBI-d study, having reviewed the application under a priority review designation. In July 2015, the FDA also granted priority review for the regular approval of the trametinib + dabrafenib combination following reporting of updated results from the COMBI-d study.[18]

[c] Grade 2 is the maximum grade that can be assigned to alopecia according to the NCI-CTCAE; alopecia cannot be assigned as Grade 3 in severity.

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

Section key points:

- Melanoma is an aggressive form of skin cancer arising from malignantly transformed melanocytes; it accounts for >80% of deaths associated with skin tumours.
- Approximately 13,000 new cases of melanoma are diagnosed in England each year and nearly 2,000 people die from the disease.
- The incidence of melanoma is disproportionately high in younger people and it is the second most common cancer in people aged 25 to 34 years in the UK.
- Melanoma has a high metastatic potential and may spread to involve any organ.
- Around 20% of primary melanomas will progress to metastatic disease which continues to have a poor prognosis despite the introduction of targeted therapies.
- Approximately 45-50% of melanomas carry activating mutations in the BRAF oncogene, the presence of which has been associated with an increased risk of mortality and shortened survival.
- Melanoma leads to more years of life lost (YLL) overall than most other common cancers (an average of 23 YLL for those with metastatic disease) and is therefore associated with a significant societal impact
- Patients with metastatic disease are often symptomatic with a consequent low quality of life and high level of impairments to physical and mental/emotional health.
- The current standard of care for patients with BRAF V600 mutation-positive metastatic melanoma is BRAF inhibitor monotherapy with either dabrafenib or vemurafenib.
- However, the longer-term efficacy of single-agent BRAF inhibitors is limited by emergence of intracellular resistance to their effects; disease progression is common within 7 months of treatment initiation and median survival is still under 2 years.
- Trametinib + dabrafenib combination therapy provides a new therapeutic strategy for this population and offers a median extension to life of at least 6 months, compared to BRAF inhibition alone. It is estimated that the maximum number of patients eligible for treatment in England is 992 annually.

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 one type of skin cancer; the other main types being basal cell carcinoma and squamous cell carcinoma. It arises from the malignant transformation of melanocytes (melanin-producing cells) and approximately 90% of melanomas have a cutaneous origin.[50; 51] Although representing less than 5% of skin cancers overall, malignant melanoma is the most aggressive form of skin cancer and can be fatal, particularly if the disease is not detected and treated at an early stage.[51]

There is a complex interaction of environmental and genetic risk factors in developing melanoma including: acute exposure to sunlight and UV radiation; having a high number of moles (naevi); being fair skinned (especially with fair or red hair); having lighter eye colour; and family history of melanoma.[52; 53]

The incidence of melanoma has been rising steadily in western populations over several decades[51]; incidence rates in the UK alone have at least quadrupled over the last 30 years.[3] This increase may be partly attributed to increased surveillance and early detection, as well as changes in diagnostic criteria, but also may reflect changes over time in people's sun-related behaviour, including use of sun-beds.[51]

Malignant melanoma is currently the fifth most common cancer in the UK, accounting for 4% of all new cancer cases.[3] In 2013, 12,246 new cases of malignant melanoma were diagnosed in England[1] and nearly 2,000 people died from the disease[2], representing 1% of all cancer deaths and 80% of deaths from skin cancer.[54]

Melanoma disease course

Several classifications have been developed to describe how deeply a melanoma has grown into the skin and whether it has spread to regional lymph nodes or distant (metastatic) sites.[55; 56] The American Joint Commission on Cancer (AJCC) system now forms the most widely used melanoma staging system. It groups patients into four stages (I to IV) that reflect the progression of melanoma, based on its thickness, the extent of any spread to regional lymph nodes or other parts of the body, and the presence of skin ulceration.[57]

A melanoma often has a slow early growth phase, and if detected before it has spread, can be cured by surgical resection. Approximately 80-90% of melanomas are diagnosed as localised tumours (Stages I and II) without regional or metastatic spread and can be dealt with in this way.[57; 58; 59] However, melanoma is an unpredictable tumour and may spread to nearby lymph nodes (Stage III) or to other parts of the body (Stage IV). Stage IV disease is further sub-divided into three M categories based on site(s) of metastases and serum levels of lactate dehydrogenase (LDH): M1a, patients with metastases in the skin, subcutaneous tissue or distant lymph nodes and normal LDH; M1b, patients with metastases to the lung and normal LDH; M1c, patients with metastases to any other visceral sites and normal LDH, or patients with metastases at any location but with an elevated LDH level.[57]

While the minority of patients (<5%) present with distant metastases at initial diagnosis[5; 50], at least 18% of primary melanomas will progress to metastatic disease.[58; 60] The prognosis in these cases is poor (discussed in Section 3.4).

Signalling pathways in melanoma

Melanoma is a complex genetic disease, and multiple genetic alterations have been reported to play a role in disease progression. The dysregulation of MAPK signalling has been shown to be one of these key drivers of the disease.[61] Approximately 45-50% of melanomas carry a mutation in the gene encoding BRAF[9; 10], a critical component in the MAPK pathway which regulates normal cell growth, differentiation and survival.[32] Mutations of BRAF, which most commonly occur at codon 600[10], cause constitutive activation of the pathway leading to melanocyte proliferation and survival, and subsequently to tumour growth.

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

Melanoma disproportionately affects a younger population than other cancers, resulting in a significant impact for patients, family and wider society. Approximately 27% of cases diagnosed with melanoma in the UK between 2009 and 2011 were in patients aged less than 50 years, while 24% of cases affected patients aged 75 and over. This compares with 11% and 36%, respectively, when considering all cancers combined (excluding non-melanoma skin cancer).[3]

Given its life-threatening nature, a diagnosis of metastatic melanoma strongly impacts patients' life expectancy and health-related quality of life (HRQoL). Although HRQoL is impacted in melanoma patients across all disease stages, patients with advanced disease have worse HRQoL than those with earlier-stage disease.[62; 63] The effect of melanoma on HRQoL is at least comparable to that observed in other cancers. Low levels of HRQoL in melanoma patients have been associated with poor recovery following surgery, reduced ability to cope with systemic therapy, and an increase in morbidity and even disease progression.[64]

Commonly reported HRQoL impairments in melanoma include decrements in physical, social and emotional/mental functioning, with deterioration in these areas over time.[8; 65; 66] The emotional impact can be long lasting and profound, with common reactions being anxiety, stress, depression and fear of isolation.[67; 68] Women report greater levels of psychological distress than men.[69]; areas of particular concern include surgical scarring and disfigurement.[8; 70]

Patients with metastatic melanoma can also suffer bothersome disease-related symptoms and health issues, including pain, fatigue, shortness of breath, insomnia / sleeping problems, headaches, appetite loss, stomach cramps, and blood in stools.[7; 8] In addition, they will likely experience adverse effects related to their treatment which may cause discomfort, distress and impact negatively on quality of life.[71; 64]

While on treatment, they may also incur travel costs associated with hospital attendances and GP visits, and costs related to lost earnings from time off work.[72] The purpose of treatment for patients with unresectable or metastatic melanoma is to enable patients to resume everyday tasks and activities (by slowing down the progression of disease). Although progress has been made in the treatment of metastatic melanoma over recent years with the approval of targeted therapies and new immunotherapies, the prognosis of metastatic melanoma remains poor, with a 5-year overall survival rates in the range of 10 to 20%.[5; 6; 73]

Brain metastases are common among patients with metastatic melanoma: up to 50% of patients with melanoma develop brain metastases during the course of their illness and about 20% have them at their first presentation of metastatic disease.[74; 75] The presence of brain metastases are associated with an even poorer prognosis, leading to significant morbidity, including neurological, cognitive and emotional difficulties.[76; 77]

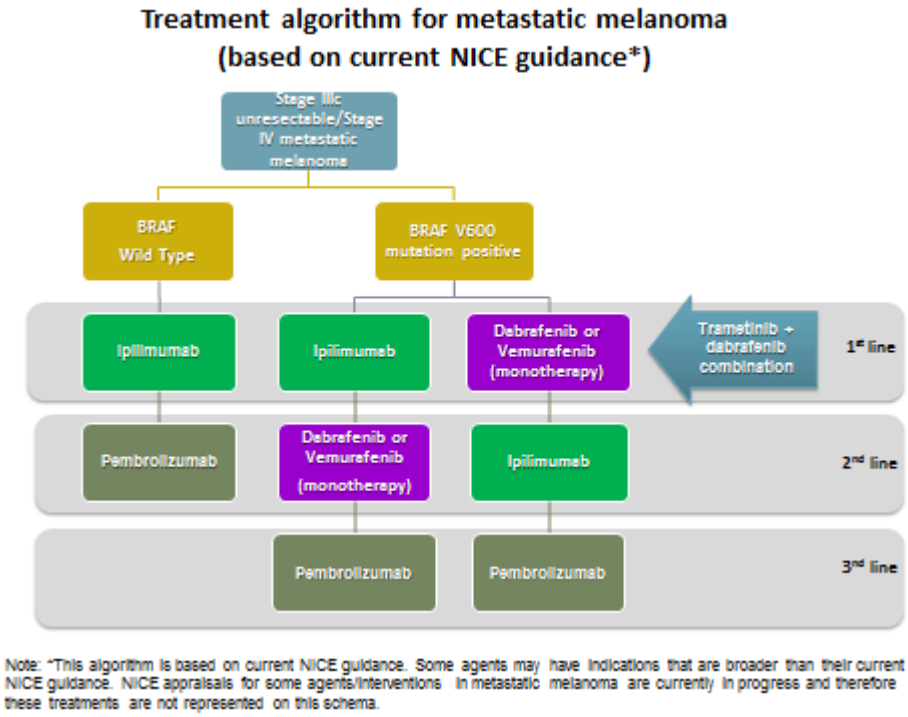
At a societal level, metastatic melanoma imposes a substantial financial cost both to the health care system and to the wider economy due to premature morbidity and mortality.[78] The total cost associated with malignant melanoma in England in 2002 was estimated as £138.4 million, with the majority attributable to indirect morbidity and indirect mortality costs. From this figure, 14.7% related to costs incurred by the NHS for the management of these patients while the remainder comprised costs borne by patients (2.6%), lost working days due to individuals' inability to function in their usual role (15.1%) and lost working life-years due to deaths (67.6%).[72]

A more recent study focussed specifically on healthcare costs highlighted the significant financial burden placed by melanoma on the NHS. The cost of managing melanoma in England was estimated at between £22.2 and £22.6 million per annum in 2008, comprising GP consultations, inpatient stays, day cases and outpatient attendances.[79]

3.3. Present the clinical pathway of care that shows the context of the proposed use of the technology. This information may be presented in a diagram. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this point should be consistent with the guideline and any differences should be explained.

The combination of trametinib + dabrafenib represents a new treatment option for patients with unresectable or metastatic melanoma whose tumours carry a BRAF V600 mutation (see Figure 2).

Figure 2: Treatment algorithm for metastatic melanoma with proposed positioning for trametinib + dabrafenib



The past 5 years has seen important advances in systemic treatments for patients with unresectable or metastatic melanoma. Prior to this, options were limited and all patients were usually offered dacarbazine which is associated with low response rates and has not demonstrated a significant survival benefit.[80] The introduction of targeted BRAF inhibitors was a step change in treatment for patients with BRAF-mutant metastatic melanoma and the clinical care pathway for metastatic melanoma is now largely determined by tumour genotype.

BRAF mutation-positive melanoma

According to current NICE technology appraisal guidance, patients identified as BRAF mutation-positive are eligible to receive treatment with a BRAF inhibitor, either dabrafenib (Tafinlar®; Novartis)[81] or vemurafenib (Zelboraf®; Roche).[82] Ipilimumab (Yervoy®; BMS), a monoclonal antibody which enhances T-cell activation, is also recommended for previously untreated unresectable or metastatic melanoma (without regard for BRAF status).[83] A BRAF inhibitor may be more likely chosen as the first-line option in patients with BRAF-mutated disease at risk of rapid progression, given that it can take weeks to months to build a complete immune response against a tumour with ipilimumab.[84] However, there are currently no prospective data from clinical trials that have established the optimally sequencing of a BRAF inhibitor and immunotherapy.[85] Recent market research (2015) commissioned by Novartis confirms that the majority of patients (>70%) with BRAF mutation-positive metastatic melanoma in the UK are receiving first-line treatment with a single-agent BRAF inhibitor with only a small proportion (<5%) receiving ipilimumab[d].[12]

[d] Remaining patients receive chemotherapy, best supportive care or are entered into a clinical trial.

Dabrafenib and vemurafenib have been accepted as having comparable efficacy but different safety profiles.[73; 81; 86; 87] Both agents in monotherapy achieve tumour response rates of approximately 60% and have shown significantly improved PFS compared with dacarbazine. However, acquired resistance to BRAF inhibition frequently develops through reactivation of the MAPK pathway, resulting in a median PFS of around 7 months.[14; 15] Trametinib monotherapy has also demonstrated clinical benefit through significant improvements in PFS and OS versus chemotherapy.[41]

The combination of dabrafenib + trametinib is designed to inhibit the MAPK pathway at two discrete points, with the aim of suppressing the resistance that typically occurs after single-agent BRAF inhibition. The clinical utility of these two agents is further optimised by their use in combination through reducing the incidence of hyperproliferative skin toxicities that characteristically arise with BRAF inhibitor therapy from paradoxical activation of the pathway, as well as by achieving significant increments in PFS, OS and response rates together with clinically meaningful improvements in HRQoL, compared with using dabrafenib or vemurafenib alone.[18; 20; 28; 29]

Figure 2 above illustrates the potential place of trametinib + dabrafenib combination therapy in the treatment pathway for metastatic melanoma, based on current NICE guidance.

In view of the evidence of the clear clinical benefits associated with using combination therapy with a MEK inhibitor + a BRAF inhibitor over a single-agent BRAF inhibitor, and assuming there are no additional reasons (contraindications or cautions) precluding the use of combination therapy in patients who would otherwise be considered for monotherapy, it is expected in the context of a positive NICE recommendation that MEK inhibitor + BRAF inhibitor combination therapy would largely replace the use of BRAF inhibitor monotherapies.

BRAF wild-type melanoma

For patients with BRAF wild-type (BRAF V600 mutation-negative) melanoma, ipilimumab is currently a recommended first-line treatment option.[83] Newer immunotherapeutic agents targeted against programmed death-1 protein (PD-1) have been licensed for the treatment of advanced melanoma in the past 6 months (nivolumab [Opdivo®, BMS]; pembrolizumab [Keytruda®, MSD]).

A Final Appraisal Determination (FAD) has recently been issued by NICE recommending pembrolizumab for advanced melanoma that has not previously been treated with ipilimumab (again, without regard for BRAF status).[88] Pembrolizumab was not a comparator stated in the scope for this appraisal and nor should it be treated as such, since the recent FAD has yet to be implemented as technology appraisal guidance; thus, it is not an agent that is in current usage within the NHS.

(Note: NICE-recommended options beyond first-line currently include ipilimumab and pembrolizumab (a PD-1 inhibitor)[89; 90] (see section 3.5).

3.4. Provide information about the life expectancy of people with the disease or condition in England and the source of the data.

Melanoma has a substantial impact on life expectancy. It typically affects a younger cohort of patients compared with many other cancers and it is the second most common cancer in adults aged between 25 and 34.[91] More than 900 adults under 35 years of age are now diagnosed with melanoma annually in the UK.[39]

A UK study reported that melanoma (a mixed BRAF wild-type and mutant population) results in an average of 15.1 years of life lost (YLL) per patient and ranked it fourth in terms of YLL among cancers examined.[92] For metastatic melanoma this figure has been estimated as 23.2 years[77], positioning the condition as one of the leading causes of lost years of life due to cancer. Assuming the population in these studies to be representative of the overall UK population, the total YLL lost is likely to be considerable given that there are over 2,000 deaths from melanoma each year.

The prognosis of melanoma varies widely depending on stage of the disease at clinical presentation. Early-stage melanoma confined to the skin is potentially curable by surgical resection with correspondingly favourable survival rates. The outlook for stage III melanoma patients is highly variable depending on nodal involvement; 5-year survival rates are the region of 40% for patients with unresectable stage IIIc disease.[57] Stage IV melanoma has an extremely poor prognosis; patients with disseminated disease can have 5-year survival rates ranging from 20% down to just 5%.[4; 5; 6; 73; 91]

Historically median survival times after stage IV diagnosis were cited in the range of 6 to 12 months depending on the organs involved[4; 59], but these are improving with the advent of new targeted and immuno- therapies. Melanoma patients who develop non-pulmonary visceral metastases continue to have the worst prognosis; in particular, life expectancy for those with brain metastases is only 3 to 5 months.[59] This is a particular concern given the marked propensity of melanoma to metastasize to the brain.[74]

The BRAF V600 mutation, present in approximately 45-50% of melanomas, has been found to increase the risk of mortality by 1.7 times[11] and is also associated with shortened survival time in metastatic disease[10] as well as a significantly younger age at diagnosis of first distant metastasis (mean 56 years vs. 63 years), compared with having BRAF wild-type melanoma.[10]

The introduction of agents targeted at mutant BRAF therefore marked a step change in the management of BRAF V600 mutation-positive melanoma, although even with these treatments, life expectancy is still under two years. Latest median OS data in the Phase III BRAF inhibitor monotherapy studies is reported to be 13.6 and 20.1 months, for vemurafenib- and dabrafenib-treated patients, respectively.[16; 93]

Now the availability of trametinib + dabrafenib combination therapy provides an opportunity to extend survival for patients with this dismal condition by more than 6 months compared with the current standard of care (vemurafenib or dabrafenib as monotherapy[e]), and thus

[e] COMBI-v: Median OS trametinib + dabrafenib 25.6 months vs. Vemurafenib 18.0 months;
COMBI-d: Median OS trametinib + dabrafenib 25.1 months vs. Dabrafenib 18.7 months.

given the small population involved (less than 1000 patients annually, see calculation below), this intervention meets the criteria for a life-extending treatment at end of life.

Please provide information on the number of people with the particular therapeutic indication for which the technology is being appraised. If the marketing authorisation also includes other therapeutic indications for the technology, provide information about the numbers of people with these diseases or conditions in England and provide the source of the data. This is to assess whether the technology may be suitable for consideration as a 'life-extending treatment at the end of life' as described in section 6.2.10 of the NICE guide to the methods of technology appraisal.

We estimate that the *maximum* number of patients covered by the therapeutic indication for trametinib + dabrafenib combination therapy (adults with unresectable or metastatic melanoma with a BRAF V600 mutation) to be 992 incident cases per annum in England (comparable to estimates provided in the manufacturer's submission for vemurafenib and in GSK's submission for dabrafenib in the same patient population) (see Table 8 below for calculation method).

It should be noted that the combination of trametinib + dabrafenib does not currently have other licensed therapeutic indications.

Table 8: Calculation of number of patients covered by therapeutic indication for trametinib + dabrafenib

	Patient numbers	Source
Annual incidence of malignant melanoma in England (2013 data for ICD-C43 registrations)	12,246	England: Office for National Statistics. Cancer Registration Statistics, England, 2013.[1] Available at: http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--44--2013/stb-cancer-registration-2013.html
Proportion of UK patients who develop unresectable (stage IIIc) /metastatic (stage IV) disease = 20%*	2449	Lacy KE, *et al*. Clinical Medicine (Journal of the Royal College of Physicians) 2012; 12: 168-171.[58] Available at: http://www.clinmed.rcpjournal.org/content/12/2/168.full.pdf+html
Proportion of UK patients with metastatic melanoma who are BRAF V600 mutation-positive = 45%	1102	(i) Melanoma Market Demand Study, conducted by Hall & Partners for Novartis. Quantitative report: UK data set. March 2015.[12] (ii) Biotrends Research Group. Treatment Trends: Melanoma (EU5). UK data set. November 2013.[13]
Proportion of UK BRAF mutated metastatic melanoma patients who receive first-line systemic therapy = 90%	992	Melanoma Market Demand Study, conducted by Hall & Partners for Novartis. Quantitative report (UK data set). March 2015.[12]

	Patient numbers	Source
Maximum total eligible population in England per annum†	**= 992**	

* assumes progressed from earlier stages of disease, plus new presentations of unresectable (Stage IIIc) / metastatic (Stage IV) disease.
† does not account for market share and assumes all eligible patients receive this targeted therapy combination.

3.5. Provide details of any relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being used. Specify whether any subgroups were explicitly addressed.

Details of relevant NICE guidance for melanoma treatments are provided below. All these recommendations were contingent on the medicine being provided to the NHS at the discount agreed in the associated patient access scheme (PAS).

- In December 2012, NICE recommended vemurafenib (Zelboraf®, Roche) as a treatment option for BRAF V600 mutation-positive unresectable or metastatic melanoma.[82]
- At a similar time, ipilimumab (Yervoy®, Bristol-Myers Squibb) was recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy.[89]
- In July 2014, ipilimumab was further recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma.[83]
- In October 2014, NICE recommended the use of dabrafenib (Tafinlar®, Novartis) as an option for treating unresectable or metastatic BRAFV600 mutation‑positive melanoma.[81]
- In October 2015, pembrolizumab was recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults only (i) after the disease has progressed with ipilimumab and (ii) for BRAF V600 mutation‑positive disease, after ipilimumab and a BRAF or MEK inhibitor.[90]
- Most recently, a Final Appraisal Determination was issued recommending pembrolizumab as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab.[88]

Additionally, guidance on the development of cancer services for people with skin tumours (including melanoma), focusing mainly on the organisation of services, was issued by NICE in 2006.[94] It pre-dated the emergence of targeted therapies and recommended non-surgical treatment options including dacarbazine and interferon-α. When the guidance was updated in October 2011, it mentioned ongoing technology appraisals for ipilimumab and vemurafenib and referenced their corresponding key clinical trials.[95]

An updated NICE clinical guideline for the assessment and management of malignant melanoma was published in July 2015.[39] The guideline recommends that genetic testing

should be offered if systemic targeted therapy is a treatment option, and in relation to the management of stage IV melanoma, advises the use of dabrafenib or vemurafenib for patients with BRAF V600 mutation-positive melanoma consistent with NICE's Technology Appraisal Guidance.[81; 82]

3.6. Provide details of other clinical guidelines (for example, UK guidance from the royal societies or European guidance) and national policies.

Details of other clinical guidelines and national policies are summarised below (in reverse chronological order):

- Clinical practice guidelines from the European Society for Medical Oncology (ESMO) for the diagnosis, treatment and follow-up of cutaneous melanoma were updated recently (2015). They comment that with the introduction of several new therapeutic strategies for metastatic melanoma the options for first-line systemic treatment are under debate, but combinations of BRAF inhibitors with MEK inhibitors are a reasonable approach for BRAF-mutated melanomas, stating "*BRAFi/MEKi inhibitor combos offer high response rates (70%) and rapid response induction associated with symptom control, with a progression-free survival (PFS) of ~12 months*."[96]
- The combination of trametinib + dabrafenib has been integrated into the most recent version of the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Melanoma (version 3.2015) as the preferred systemic therapy option for patients with unresectable/metastatic BRAF V600 mutant disease. Alternative treatments include dabrafenib or vemurafenib as monotherapy.[97]
- An European consensus-based multi-disciplinary guideline, written under the auspices of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC), was published in 2012.[59] Although the guideline established that a treatment algorithm for stage IV melanoma could not be established at that time due to insufficient data, it stated that BRAF V600 mutation-positive patients should be offered treatment with BRAF inhibitors in the context of clinical trials, while those experiencing progression on first-line treatment and with a health status expected to lead to at least 6 months of survival should be offered ipilimumab.
- Other UK guidelines for cutaneous melanoma include those drawn up by a multi-disciplinary group coordinated by the British Association of Dermatologists (BAD) and the Melanoma Study Group (MSG). Published in 2010 before the introduction of targeted therapies, these guidelines recommend dacarbazine as the standard treatment for patients with stage IV disease outside of clinical studies, with the acknowledgement that no survival benefits have been shown in patients with advanced melanoma.[98]
- Previously BAD had developed concise guidelines for the management of melanoma in conjunction with the Royal College of Physicians (RCP) (2007).[53] These guidelines are now superseded by more up-to-date UK guidelines for melanoma such as the NICE

clinical guideline 2015, based on the latest available clinical evidence and expert consensus gathered from healthcare professionals working in this field.

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

We are not aware of any issues or uncertainty relating to current clinical practice for the population under consideration. Both dabrafenib and vemurafenib have been the subject of positive NICE guidance for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma[81; 82], such that BRAF inhibitor monotherapy is now the accepted standard of care in this patient group. This has been supported by the recent NICE clinical guideline which provides clear recommendations for genetic testing where targeted therapy is a treatment option, and the use of dabrafenib or vemurafenib in patients with stage IV melanoma and a BRAF V600 mutation.[39]

3.8. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information about equality issues see NICE's equality scheme.

Provide an assessment of whether the use of this technology is likely to raise any equality issues. Please document if there are any potential issues that:

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for whom the technology is or will be licensed**
- **could lead to recommendations that have a different impact on people protected by the equality legislation compared with the wider population, for example by making it more difficult in practice for a specific group to access the technology**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.**

- **Please provide any evidence that would enable the Committee to identify and consider the impact of equality issues. State how the analysis has addressed these issues.**

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

4. Clinical effectiveness

Section key points:

- A systematic review identified three RCTs for the combination of trametinib + dabrafenib versus the comparators for this appraisal, dabrafenib and vemurafenib as monotherapy: two Phase III studies, COMBI-d (MEK115306) versus dabrafenib, and COMBI-v (MEK116513) versus vemurafenib, plus a supportive Phase II study BRF113220 (Part C) versus dabrafenib, in nearly 1,300 patients with BRAF V600 mutation-positive metastatic melanoma.
- The comparative efficacy and safety evidence for trametinib + dabrafenib combination therapy versus the two comparators comes primarily from the robust phase III head-to-head studies which had very similar study designs and enrolled highly comparable patient populations.

Efficacy (Phase III studies)

- Trametinib + dabrafenib showed statistically significant and clinically meaningful reductions (of approximately 30%) in both the risk of disease progression or death, and the risk of death, compared with BRAF inhibitor monotherapy.
- Median overall survival (OS) for the combination was approximately 25 months which was at least 6 months longer than for dabrafenib or vemurafenib monotherapy. More than half of patients were still alive on combination therapy after 2 years compared with 38-42% on BRAF inhibitor monotherapy.
- Median progression-free survival (PFS) was also significantly prolonged with trametinib + dabrafenib combination therapy and in the range of 11.0 to 12.6 months, compared with dabrafenib (8.8 months) or vemurafenib (7.3 months) monotherapy.
- Overall responses rates (ORR) were significantly higher (66-69% vs. 53%) and median duration of response was longer (more than 1 year) for the combination of trametinib + dabrafenib compared with dabrafenib or vemurafenib monotherapy.
- HRQoL assessments demonstrated that patients receiving trametinib + dabrafenib combination therapy experienced statistically significant and clinically meaningful improvements in many aspects of HRQoL (global health status, functional and symptomatic dimensions) compared with those on BRAF inhibitor monotherapy.

Safety

- The safety profile of trametinib + dabrafenib combination therapy is well-characterised and manageable with appropriate interventions (as recommended on the SPCs).
- The most common adverse events (AEs) for trametinib + dabrafenib combination therapy (occurring in ≥ 20% patients in the clinical studies) include: pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, and vomiting.
- Approximately half of the AEs experienced by patients on combination treatment were Grades 1 and 2. Grade 3/4 AEs occurred in 50% and 57% of patients on combination therapy in the Phase III studies (compared with 45% and 66% on dabrafenib and vemurafenib monotherapy respectively).
- Pyrexia is the most notable AE associated with the combination of trametinib + dabrafenib, and is more frequent than with dabrafenib alone. However, ≤7% of patients experienced Grade 3 pyrexia in the clinical studies and there were no Grade 4 events. Most cases of pyrexia can be simply managed with anti-pyretic medication and/or treatment interruption; ≤4% of pyrexia events led to treatment discontinuation.
- The incidence of skin-related toxicities (e.g. hyperkeratosis, hand-foot syndrome, alopecia, skin papilloma, cutaneous squamous cell carcinoma) associated with BRAF inhibitor therapy is reduced through the addition of trametinib to dabrafenib. Photosensitivity reactions (4% vs. 23%) and arthralgia (27% vs. 52%) were also less frequent with trametinib + dabrafenib than with vemurafenib. This attenuation in AEs may contribute to the positive perception of HRQoL by patients on the combination given the physical, psychological and/or quality-of-life impact of some of these conditions.
- AEs of special interest (all grade) occurring in patients receiving trametinib + dabrafenib included but were not limited to: cuSCC (including keratoacanthoma) (≤3%); dermatitis acneiform (≤10%), decrease in ejection fraction (≤8%); chorioretinopathy (≤1%); non-cutaneous malignancies (1%); new primary melanoma (<1%).
- Discontinuation rates due to AEs were 9-16% across the trials indicating that the majority of patients could remain on combination therapy, with their AEs being managed through dose reductions/interruptions.

4.1. Identification and selection of relevant studies

Provide the information specified in sections 4.1.1–4.1.6.

4.1.1. Advise whether a search strategy was developed to identify relevant studies for the technology. If a search strategy was developed and a literature search carried out, provide details under the subheadings listed in this section. Key aspects of study selection can be found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

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

The overall objective of the systematic review was to evaluate the efficacy and safety of the combination of trametinib + dabrafenib (the intervention under review), compared with first-line or second-line treatments for patients with metastatic melanoma. Only data relating to trametinib + dabrafenib, and its comparison with dabrafenib and with vemurafenib (the comparators defined in the scope for this appraisal), in patients with BRAF V600 mutation-positive melanoma are relevant to the decision problem and presented in this submission document.

Search strategy

4.1.2. Describe the search strategies used to retrieve relevant clinical data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided so that the results may be reproduced. This includes a full list of all information sources and the full electronic search strategies for all databases, including any limits applied. The search strategies should be provided in an appendix.

A comprehensive search strategy was designed to retrieve clinical data of relevance to the submission from the published literature. The following electronic biomedical databases were searched from database inception to 13 July 2015 (Table 9).

Full details of the electronic search strategies and search syntax for the individual databases/sources are provided in Appendix 8.2. The full Systematic Review report is available upon request.

Table 9: Databases searched for the clinical review and the search platform

Data source	Search cut-off date	Service provider
MEDLINE (1980 onwards)	13 July 2015	Embase.com http://www.embase.com/
MEDLINE In process and other non-indexed citations (1980 onwards)	13 July 2015	PubMed http://www.ncbi.nlm.nih.gov/sites/entrez
EMBASE (1980 onwards)	13 July 2015	Embase.com http://www.embase.com/
Cochrane Central Register of Controlled Trials (CENTRAL)	13 July 2015	Cochrane library http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html

The following conference proceedings were hand-searched for 2012 to October 2015 in order to retrieve studies that have not yet been published in journals or to supplement previously published studies:

- American Society of Clinical Oncology (ASCO)
- European Society of Medical Oncology (ESMO)/European CanCer Organization (ECCO)
- International Melanoma Congress presented by the Society for Melanoma Research (SMR)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Additional data reported in public assessment reports were searched from the European Medicines Agency (EMA) and Food and Drug Administration (FDA) websites. Further, Health Technology Assessment (HTA) guidance documents published in English were searched from the National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), and other relevant HTA organisations.

Study selection

4.1.3. Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process in a table. Justification should be provided to ensure that the rationale for study selection is transparent. A suggested table format is provided below.

Details of the inclusion and exclusion criteria employed for the systematic review are presented in Table 10. The comparators for this appraisal are dabrafenib and vemurafenib as monotherapies; however, the full systematic review included other targeted and immunotherapy agents used in the treatment of metastatic melanoma. Only data relating to the comparison of trametinib + dabrafenib versus dabrafenib or vemurafenib are reported in this submission.

Table 10: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Rationale for inclusion
Population	• Age: adults aged ≥18 years • Gender: any • Race: any • Disease: patients with unresectable or metastatic malignant melanoma • Line of therapy: First or second line of therapy for the metastatic stage	• Studies that included patients <18 years, or that did not provide sub-group data for the adult populations. • Studies that included melanoma patients with varying disease stages, but did not provide sub-group data for patients with metastatic disease. • Studies which recruited patients with all lines of therapy but did not provide sub-group data for patients on first-line or second-line of treatment. • Studies that included patients with metastatic melanoma, but did not provide sub-group data for patients with BRAF mutation positive subtype. • Studies in patients with other types of skin cancers (non-melanoma skin cancers, such as basal cell and squamous cell cancers, Kaposi sarcoma, and lymphoma of the skin).	• Mean age of diagnosis is 50 years; approximately 20% of melanoma cases occur in young adults aged between 15 years and 39 years. • Melanoma can occur both in men and women, although men are at a higher risk. • Clinical trials and other studies usually enrol participants of all races to have a sample population representative of the larger population, and to reduce bias.
Intervention	• Trametinib + dabrafenib • Dabrafenib • Trametinib • Vemurafenib + cobimetinib • Vemurafenib • Ipilimumab • Nivolumab • Pembrolizumab	• Any other intervention. • Studies that investigated multiple interventions and did not provide sub-group data for the intervention(s) of interest	• These interventions were identified from clinical practices or from ongoing clinical trials for treatment of metastatic malignant melanoma.
Comparators	• Any included intervention • Placebo/BSC • Any chemotherapy /immunotherapy	• Any other comparison. • Studies that investigated multiple comparisons and did not provide sub-group data for the comparison(s) of interest	• These comparators were selected to potentially enable both direct and indirect comparisons between the interventions of interest.

Outcomes	*Efficacy*: • Overall survival (OS) • Progression-free survival (PFS) • Overall response rate (ORR: Complete response [CR] + Partial response [PR]) • Proportion of patients with stable disease (SD), and progressive disease (PD) • Time to, and duration of, response (TtR, DoR) • Health-related quality of life (HRQoL) *Safety*: • Incidence and severity of adverse events (AEs) generally • Incidence and severity of specific AEs of interest • Withdrawals due to AEs • Withdrawals due to death • Incidence of serious adverse events (SAEs)	• Any study that did not include at least one of the included outcome measures	• These outcomes were chosen since they are frequently measured and reported in trials in metastatic melanoma. • Refer to Table 14 and Section 4.13.2 for justification and further explanation relating to the selection of these study outcomes.
Study design	• Randomised controlled trial (RCT)	• Any other study design e.g. non-randomised clinical trials, prospective and retrospective observational studies, case studies/series etc.	• RCTs are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of interventions. To enhance the level of evidence, studies with double-blind, single-blind, and open label design were included.
Language restrictions	• English	Any other language	• Language restriction was not expected to limit results substantially and data was available in English language.

4.1.4. A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses, such as the PRISMA flow diagram. The total number of studies in the statement should equal the total number of studies listed in section 4.2.

Citations retrieved through the literature search were initially screened for inclusion based on their title and abstract. Citations that did not match the eligibility criteria were excluded at this 'first pass', as were duplicates of citations. Full-text copies were obtained for citations that met the inclusion criteria and also where it was not possible to determine whether the study met the inclusion criteria based on the abstract alone. The full-text publications were then screened with more specific eligibility criteria. At each stage, screening was conducted by two independent reviewers, and any discrepancies were reconciled by a third independent reviewer.

Studies which met the eligibility criteria at the second screening stage were extracted in parallel by two independent reviewers and any discrepancies resolved by a third independent reviewer. Where more than one publication was identified describing a single study, the data were either compiled into a single entry to avoid duplication of data or different publications reporting subgroup data were extracted separately with their respective IDs.

Details of the flow of studies included at each step of the review are specified in the PRISMA flow diagram (Figure 3). The electronic database search yielded 4126 separate records, of which 639 references were found to be duplicates and were removed. Following first pass of the remaining 3487 citations, 194 potentially relevant references were identified. Additional references (n=27) meeting the inclusion criteria for this review were identified from conference proceedings, HTA searching, bibliographic searching and clinical study reports provided by Novartis/GSK.

Following detailed examination of these 221 articles, 139 citations were excluded for not meeting the eligibility criteria. Further details of the excluded studies are available on request. Following full-text screening and linking of multiple publications, 12 studies (reported in 82 publications) met the inclusion criteria for the clinical review.

A list of these 12 studies is provided in Table 11 below. All the included studies were active-controlled RCTs conducted in patients with unresectable or metastatic melanoma. All of the studies were conducted primarily in patients receiving first-line therapy, except the METRIC and KEYNOTE 006 studies that included pre-treated as well as treatment-naïve patients with separate data available for each sub-population.

Only 3 studies compared the technology under review, trametinib + dabrafenib combination therapy, with one of the comparators defined in the scope (dabrafenib or vemurafenib), in the population of interest (patients with BRAF V600 mutation-positive melanoma), and are therefore relevant to the decision problem:

- **BRF113220**: A Phase II trial conducted in four parts where Part C involved randomisation of patients to either one of two different dosages of dabrafenib in combination with trametinib or to dabrafenib monotherapy.[25; 26; 99]

- **MEK115306 / COMBI-d**: A Phase III RCT evaluating the efficacy and safety of trametinib + dabrafenib compared with dabrafenib monotherapy.[17; 18]
- **MEK116513 / COMBI-v**: A Phase RCT trial evaluating the efficacy and safety of trametinib + dabrafenib compared with vemurafenib monotherapy.[19; 20]

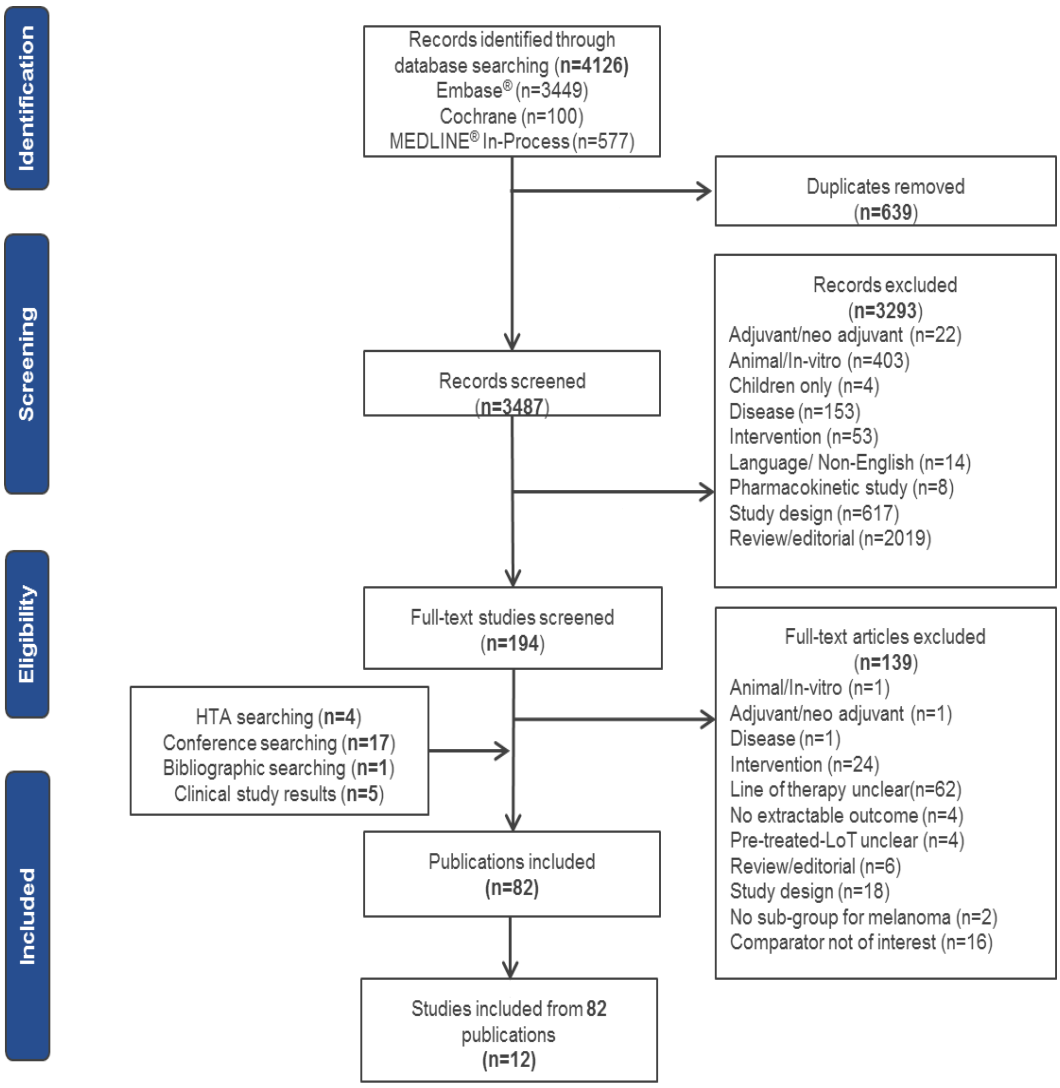
Table 11: List of all studies that met inclusion criteria for clinical review (studies shaded pale blue are those relevant to this decision problem)

Study number/ acronym	Patient numbers	Intervention	Population
A. Studies restricted to BRAF V600 mutation-positive patients			
(i) Studies assessing combination therapies			
BRF113220 Part C[25; 26]	162	• Dabrafenib 150mg b.d. (N=54) • Dabrafenib 150mg b.d.+ trametinib 1mg o.d. (N=54) • Dabrafenib 150mg bid + trametinib 2mg o.d. (N=54)	Patients with BRAF V600E/K mutation-positive metastatic melanoma, with ≤1 prior chemotherapy for advanced/metastatic disease.
MEK115306 COMBI-d[17; 18]	423	• Dabrafenib 150mg b.d.+ trametinib 2mg o.d. (N=211) • Dabrafenib 150mg b.d. + placebo (N=212)	Patients with previously untreated, unresectable or metastatic BRAF V600E/K mutation-positive melanoma.
MEK116513 COMBI-v[19; 20]	704	• Dabrafenib 150mg b.d.+ trametinib 2mg o.d. (N=352) • Vemurafenib 960 mg b.d. (N=352)	Patients with previously untreated, unresectable or metastatic BRAF V600E/K mutation-positive melanoma.
coBRIM[100; 101]	495	• Vemurafenib 960 mg b.d. + cobimetinib 60 mg o.d. (N=247) • .Vemurafenib 960 mg b.d. (N=248)	Patients with previously untreated, unresectable or metastatic BRAF V600 mutation-positive melanoma.
(ii) Studies assessing monotherapies			
BRF113683 BREAK-3[14; 16; 102]	250	• Dacarbazine 1000 mg/m^2 q3w (N=63) • Dabrafenib 150 mg b.d. (N=187)	Patients with previously untreated, unresectable or metastatic BRAF V600E mutation-positive melanoma.
BRIM-3[15; 103]	675	• Dacarbazine 1000 mg/m^2 q3w (N=338) • Vemurafenib 960 mg b.d. (N=337)	Patients with previously untreated, unresectable or metastatic BRAF V600E mutation-positive melanoma.
MEK114267 METRIC[41]	322	• Trametinib 2 mg o.d. (N=214) • Chemotherapy (N=108) (Dacarbazine 250 mg/m^2 q3w or Paclitaxel 175 mg/m^2 q3w)	Patients with BRAF V600E mutation-positive metastatic melanoma, with ≤1 prior chemotherapy for advanced/metastatic disease.
B. Studies in which patients were not selected on basis of BRAF mutational status, or studies with mixed populations of BRAF wild-type and BRAF mutation-positive patients, or studies limited to BRAF wild-type patients			
CA184-024[104]	502	• Ipilimumab 10 mg/kg + Dacarbazine 850 mg/m^2 (N=250) • Dacarbazine 850 mgm^2 (N=252)	Patients with previously untreated unresectable or metastatic melanoma
KEYNOTE 006 [105]	834	• Pembrolizumab 10 mg/kg q2w (N=279) • Pembrolizumab 10 mg/kg q3w (N=277) • Ipilimumab 3 mg/kg (N=278)	Patients with unresectable or metastatic melanoma, with ≤1 prior systemic therapy for advanced disease, and known BRAF V600 mutational status
CHECKMATE	418	• Dacarbazine 1000 mg/m^2	Patients with previously

066[106]		(N=208) • Nivolumab 3 mg/kg (N=210)	untreated unresectable or metastatic melanoma without a BRAF mutation
CHECKMATE 067[107]	945	• Nivolumab 1 mg/kg q3w + Ipilimumab 3 mg/kg q3w (N=314) • Nivolumab 3 mg/kg q2w (N=316) • Ipilimumab 3 mg/kg q3w (N=315)	Patients with previously untreated unresectable or metastatic melanoma, and known BRAF mutational status
CHECKMATE 069[108]	142	• Nivolumab 1 mg/kg q3w + Ipilimumab 3 mg/kg (N=95) • Ipilimumab 3 mg/kg (N=47)	Patients with previously untreated unresectable or metastatic melanoma, and known BRAF mutational status

b.d. = twice daily; o.d. = once daily.

Figure 3: Study flow diagram for the clinical review



4.1.5. When data from a single study have been drawn from more than 1 source (for example, a poster and a published report) or when trials are linked (for example, an open-label extension to a randomised controlled trial [RCT]), this should be clearly stated.

Data for the three RCTs that have been identified as being relevant to the decision problem (COMBI-d [MEK115306]; COMBI-v [MEK116513] and BRF113220 [Part C]) have been drawn from a number of sources, as shown in Table 12 overleaf.

Table 12: List of data sources for RCTs relevant to decision problem

Author(s)	Source	Title	Clinical cut-off date
COMBI-d (MEK115306)			
Long *et al* [109]	Oral presentation at ASCO 2014; Abstract no. 9011.	COMBI-d: A randomized, double-blinded, Phase III study comparing the combination of dabrafenib and trametinib to dabrafenib and trametinib placebo as first-line therapy in patients with unresectable or metastatic BRAFV600E/K mutation-positive cutaneous melanoma.	26 August 2013
Long *et al*[17]	New Engl J Med 2014; 371: 1877-1888.	Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma	26 August 2013
GSK/Novartis[110]	Clinical Study Report (CSR) for MEK115306 (2013N176386_00).	A Phase III, randomised, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma.	26 August 2013
Long *et al*[30]	Oral presentation at ASCO 2015; Abstract no. 102.	Overall Survival in COMBI-d: A randomized, double-blinded, Phase 3 study of dabrafenib and trametinib versus dabrafenib and placebo as first-line therapy in patients with BRAF V600E/K metastatic melanoma.	12 January 2015
GSK/Novartis[111]	Abbreviated Clinical Study Report (aCSR) for MEK115306 (2014N219061_00).	A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma	12 January 2015
Schadendorf *et al*[28]	Eur J Cancer 2015; 51: 833–840.	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.	26 August 2013
COMBI-v (MEK116503)			
Robert *et al*[112]	Abstract and oral presentation at ESMO 2014. Abstract no. LBA4_PR.	COMBI-v: A randomized, open-label, Phase III study comparing the combination of dabrafenib and trametinib with vemurafenib as first-line therapy in patients with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma.	17 April 2014
Robert *et al*[19]	New Engl J Med 2015; 372: 30-39.	Improved overall survival in melanoma with combined dabrafenib and trametinib	17 April 2014
GSK/Novartis[113]	Clinical Study Report (CSR) for MEK116513 (2014N210212_00)	A Phase III, randomised, open-label study comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma.	17 April 2014
Robert *et al*[20]	Oral presentation at European Cancer Congress 2015; Abstract no.3301.	Two-year estimate of overall survival in COMBI-v, a randomized, open-label, Phase 3 Study comparing the combination of dabrafenib and trametinib vs vemurafenib as first-line therapy in patients With unresectable or metastatic BRAF V600E/K mutation-	13 March 2015

		positive cutaneous melanoma.	
Grob *et al*[29]	Lancet Oncol 2015; 16: 1389–98	Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a Phase 3, open-label, randomised trial	17 April 2014
Bell H, Latimer N. School of Health and Related Research (ScHARR)[27]	Unpublished report	Adjusting for treatment switching in the Combi-V study, comparing dabrafenib combined with trametinib to vemurafenib in patients with metastatic melanoma: March 2015 data-cut	13 March 2015
BRF113220 (Part C)			
Flaherty *et al*[25]	New Engl J Med 2012; 367: 1694-1703.	Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations.	31 May 2012
Long *et al*[99]	Oral presentation at ESMO 2012; Abstract no. LBA27_PR.	Randomised Phase II study of BRAF inhibitor dabrafenib vs combination with MEK inhibitor trametinib in $BRAF^{V600}$ mutant metastatic melanoma.	31 May 2012
GSK/Novartis[114]	Clinical Study Report (CSR) for BRF113220 part C (2012N143453_01).	An open-label, dose-escalation, Phase IB/II study to investigate the safety, pharmaco-kinetics, pharmacodynamics and clinical activity of the BRAF inhibitor GSK2118436 (dabrafenib) in combination with the MEK inhibitor GSK1120212 (trametinib) in subjects with BRAF mutant metastatic melanoma (Part C).	31 May 2012
Daud *et al*[115]	Oral presentation at Society for Melanoma Research 2013; Abstract no. DBR-ABS-00027334.	Overall Survival (OS) Update for BRF113220 Part C, a Phase II three-arm randomised study of dabrafenib alone vs combination of dabrafenib and trametinib in pts with $BRAF^{V600}$ mutation-positive metastatic melanoma (MM).	29 March 2013
GSK/Novartis[116]	Abbreviated Clinical Study Report (aCSR) for BRF113220 part C (2014N194662_00).	An open-label, dose-escalation, Phase IB/II study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of the BRAF Inhibitor GSK2118436 in combination with the MEK inhibitor GSK1120212 in subjects with BRAF mutant metastatic melanoma.	15 January 2014
Flaherty *et al*[117]	Oral presentation at ASCO 2014; Abstract no. 9010.	Updated overall survival for BRF113220: A Phase 1-2 study of dabrafenib alone vs combined dabrafenib and trametinib in patients with BRAF V600 mutation–positive metastatic melanoma.	15 January 2014
Daud *et al*[26]	Poster presentation at ASCO 2015; Poster number 2517; Abstract no. 9036.	Updated overall survival for BRF113220: A Phase 1-2 study of dabrafenib alone vs combined dabrafenib and trametinib in patients with BRAF V600 mutation–positive metastatic melanoma.	15 January 2015
Bell H, Latimer N. School of Health and Related Research (ScHARR)[118]	Unpublished report.	Adjusting for treatment switching in Part C of the BRF113220 Phase 2 clinical trial: January 2015 data.	15 January 2015

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

A list of studies excluded from the systematic review is provide in the supporting documentation accompanying this submission.

4.2. List of relevant randomised controlled trials

4.2.1. In a table, present the list of relevant RCTs comparing the intervention with other therapies (including placebo) in the relevant patient group. Highlight which studies compare the intervention directly with the appropriate comparator(s) with reference to the decision problem.

Table 13 lists the RCTs that are relevant to this appraisal. Two RCTs, COMBI-d and BRF113220 (Part C), directly compare the intervention, trametinib + dabrafenib combination therapy, with dabrafenib monotherapy, a comparator for this appraisal as specified in the decision problem. COMBI-v study directly compares trametinib + dabrafenib with vemurafenib monotherapy, the other comparator stated in the decision problem. The two Phase III trials, COMBI-d and COMBI-v, provide the primary sources of evidence with the randomised part (Part C) of the Phase II BRF113220 study providing supportive evidence.

Table 13: List of RCTs relevant to the appraisal

Study name	Study type	N	Intervention	Comparator	Population	Primary references	Linked publications
COMBI-d **(MEK115306)**	Phase III, double-blind, RCT	423	Dabrafenib 150mg b.d.+ trametinib 2mg o.d. (N=211)	Dabrafenib 150mg b.d. + placebo (N=212)	Patients with previously untreated, unresectable or metastatic BRAF V600E/K mutation-positive melanoma.	Long *et al.* Lancet 2015[18]	Long *et al.* ASCO 2014[109] Long *et al.* NEJM 2014[17] Long *et al.* ASCO 2015[30] Schadendorf *et al.* 2015[28]
COMBI-v **(MEK116513)**	Phase III, open-label, RCT	704	Dabrafenib 150mg b.d.+ trametinib 2mg o.d. (N=352)	Vemurafenib 960 mg b.d. (N=352)	Patients with previously untreated, unresectable or metastatic BRAF V600E/K mutation-positive melanoma.	Robert *et al.* ECC 2015[20]	Robert *et al.* ESMO 2014[112] Robert *et al.* NEJM 2015[19] Grob *et al.* Lancet Oncol 2015[29]
BRF113220 **(Part C)**	Phase II, open-label 4-part study: Part C (randomised)	162	Dabrafenib 150mg b.d. + Trametinib 2mg o.d. (N=54) Dabrafenib 150mg b.d. + Trametinib 1mg o.d. (N=54)	Dabrafenib 150mg b.d. (N=54)	Patients with BRAF V600E/K mutation-positive metastatic melanoma, with up to one prior chemo-therapy for advanced/ metastatic disease.	Flaherty *et al.* NEJM 2012[25] Daud *et al.* ASCO 2015[26]	Long *et al.* ESMO 2012[99] Daud *et al.* SMR 2013[115] Flaherty *et al.* ASCO 2014[117]

4.2.2. When the RCTs listed above have been excluded from further discussion, justification should be provided to ensure that the rationale for doing so is transparent. For example, when RCTs have been identified, but there is no access to the level of data required, this should be stated.

Not applicable.

4.3. Summary of methodology of the relevant randomised controlled trials

Provide the information specified in sections 4.3.1 and 4.3.2.

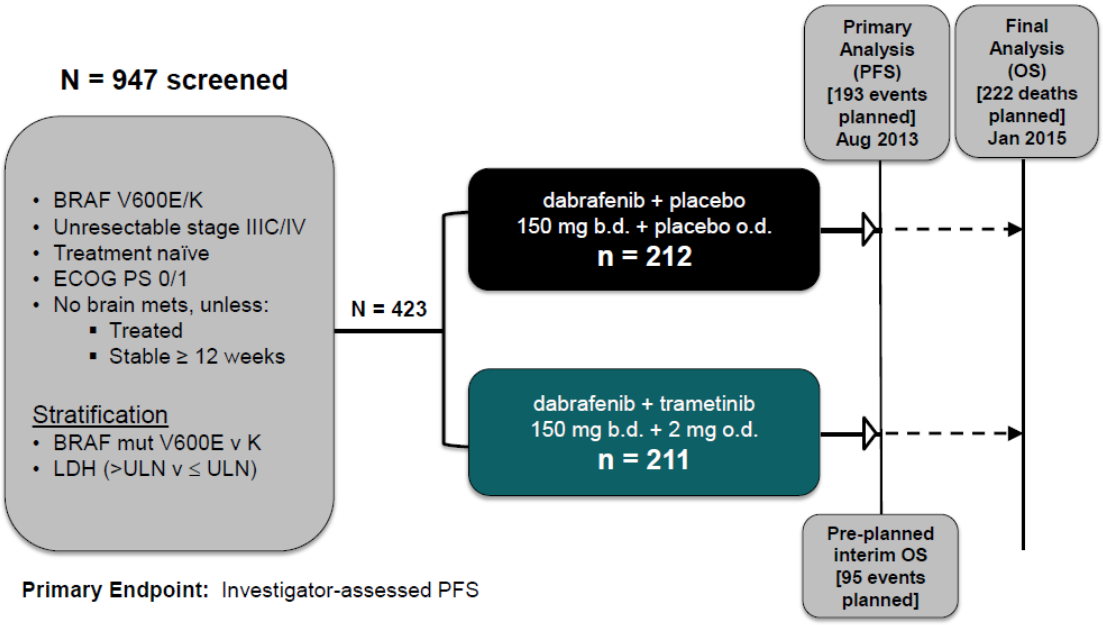
4.3.1. Items 3 to 6b of the CONSORT checklist should be provided for all RCTs listed.

COMBI-d (MEK115306) [17; 18]

The primary objective of this double-blind Phase III RCT was to establish the superiority of trametinib + dabrafenib combination therapy over dabrafenib monotherapy in patients with unresectable or metastatic BRAF V600 mutation-positive melanoma. A placebo control was added to the dabrafenib monotherapy arm to allow blinded administration of the study treatments, thereby reducing the chance of bias. The benefit of the combination over dabrafenib monotherapy was evaluated through the primary endpoint of investigator-assessed progression-free survival (PFS). Crossover was not permitted in order to preserve the integrity of the secondary endpoint of overall survival (OS). The dose used for the combination was based on the results of the Phase II BRF113220 Part C study which showed better efficacy for trametinib 2mg o.d. + dabrafenib 150 mg b.d. compared with trametinib 1mg o.d. + dabrafenib 150 mg b.d.,[25; 99] with a safety profile that could be managed with appropriate interventions.

A detailed overview of the study design and methodology of COMBI-d is provided in Table 14. Patient enrolment commenced in May 2012 and closed in January 2013. The study over-enrolled by 24% (423 subjects instead of 340 planned) because the recruitment rate accelerated towards the end of the enrolment period (see Table 15 for discussion of the statistical adjustments necessitated by the over-enrolment). Outcome data presented in this submission are from planned analyses conducted with cut-off dates of 26 August 2013 (Primary Analysis for PFS and interim OS) and 12 January 2015 (Final Analysis for OS). Follow-up is still ongoing for additional survival and safety data. A CONSORT flow diagram for COMBI-d is provided in Figure 7.

Figure 4: COMBI-d study schema



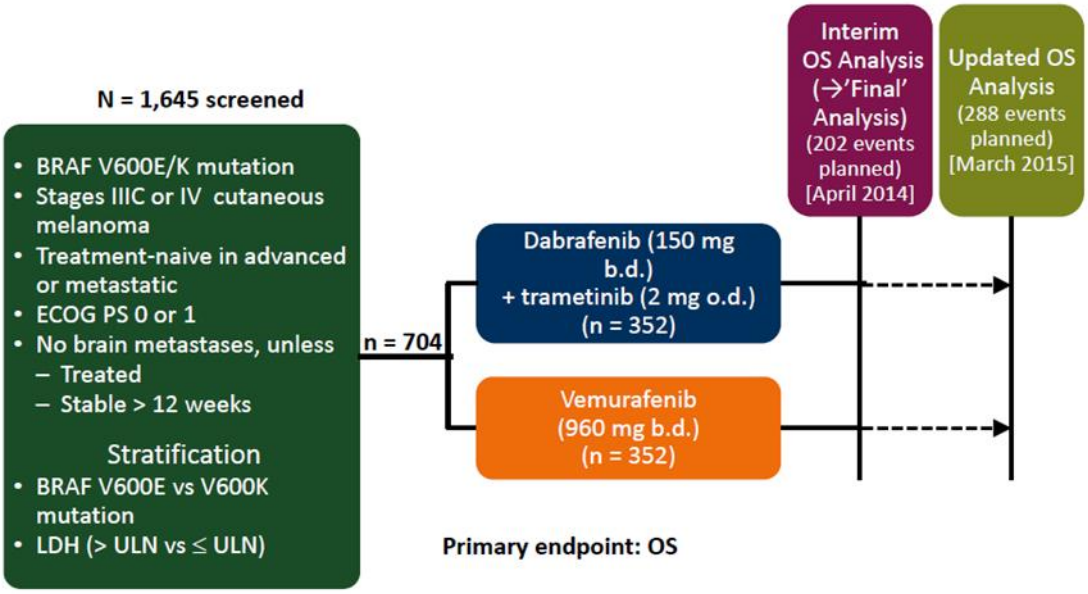
COMBI-v (MEK116513)[19; 20]

The primary objective of this open-label Phase III RCT was to establish the superiority of trametinib + dabrafenib combination therapy over vemuafenib monotherapy with respect to overall survival (OS) in patients with unresectable or metastatic BRAF V600 mutation-positive melanoma. Vemurafenib was chosen as the comparator as it was the emerging standard of care at the time the study was initiated. The dose used for the combination was the same as for the COMBI-d study (see above).

A detailed overview of the study design and methodology of COMBI-v is provided in Table 14. Patients were enrolled between June 2012 and October 2013. An interim analysis (April 2014 cut-off) demonstrated a significant increase in OS in the trametinib + dabrafenib arm compared with the vemurafenib arm. In July 2014, the study's Independent Data Monitoring Committee (IDMC) met to review the data and recommended stopping the study early due to the superior efficacy in the combination arm (the pre-specified stopping boundary [p<0.0214 for OS difference] had been crossed), and as such, the interim analysis became 'final'. A subsequent protocol amendment (August 2014) permitted patients in the vemurafenib arm to crossover to receive trametinib + dabrafenib (see section 4.4.3.2 for further details).

Outcome data presented in this submission are from the planned interim analysis conducted with a cut-off date of 17 April 2014 and an updated analysis conducted with 13 March 2015 cut-off. Follow-up is still ongoing for additional survival and safety data. A CONSORT flow diagram for COMBI-v is provided in Figure 8.

Figure 5: COMBI-v study schema

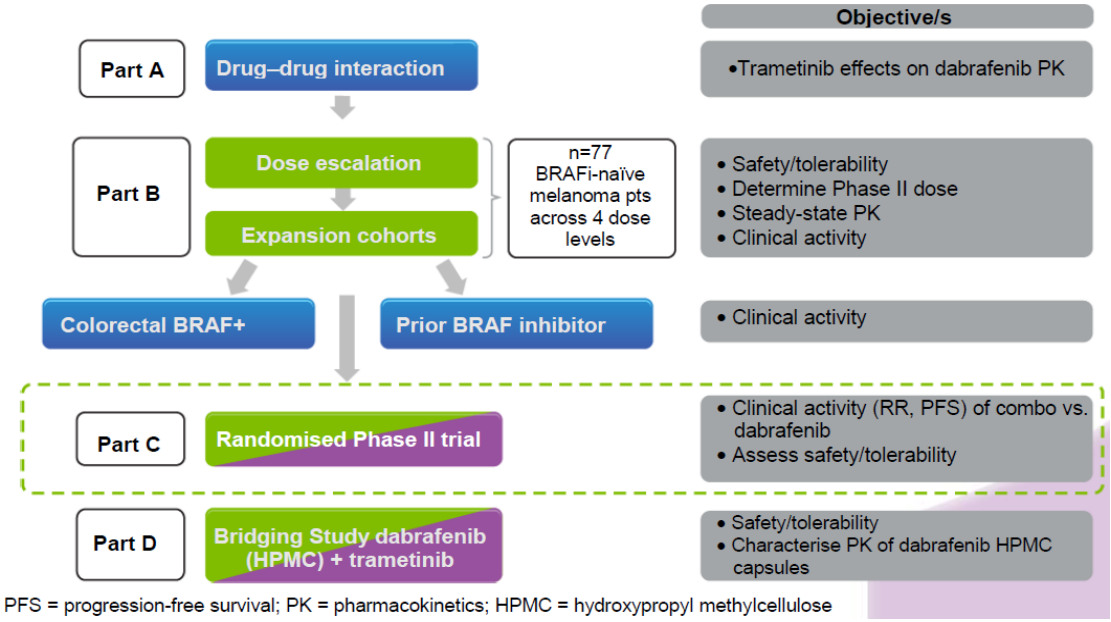


BRF113220 [25; 26; 99]

BRF113220 was a Phase I/II study to investigate the safety, pharmacokinetics, pharmacodynamics, and clinical activity of dabrafenib in combination with trametinib primarily in patients with BRAF V600 mutant metastatic melanoma. It comprised 4 parts, designated Parts A to D. Part C was initially designed as non-randomised expansion cohorts based on doses identified in Part B. The study design was amended (randomisation and a dabrafenib monotherapy arm was added) in order to facilitate a more robust evaluation of safety, tolerability and efficacy for the combination. Two experimental dose levels were chosen for the combination in Part C based on pharmacokinetic, pharmacodynamic, and tolerability data from Parts A and B; these were dabrafenib 150mg b.d. + trametinib 1mg o.d. (combination 150/1) and dabrafenib 150mg b.d. + trametinib 2mg o.d. (combination 150/2).

A detailed overview of the study design and methodology of BRF113220 Part C is provided in Table 14. Patient enrolment to Part C of the study commenced in December 2010 and completed in July 2011. Outcome data presented in this submission are from a planned analysis conducted with a cut-off date of 31 May 2012; plus additional annual survival analyses conducted with 29 March 2013, 15 January 2014 and 15 January 2015 cut-offs. Patients who progressed on the dabrafenib monotherapy control arm could crossover to receive the combination 150/2 arm upon independently-confirmed disease progression. Outcomes for this crossover group of patients are not discussed in the main body of this submission but can be found in Appendix 8.8. A CONSORT flow diagram for BRF1113220 Part C is provided in Figure 9.

Figure 6: BRF113220 study schema



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

Information to include: Trial design (including details of randomisation); Eligibility criteria (including definitions and assessments); Settings and locations where the data were collected (including country and care setting); Trial drugs and concomitant medications (including dosing information); Primary, secondary and tertiary outcomes (including time points for assessment and evidence of reliability/validity/current status of the measure).

A comparative summary of the methodology of the RCTs is provided in Table 14 overleaf. The COMBI-d and COMBI-v studies were methodologically very similar in a number of respects.

Table 14: Comparative summary of methodology of the RCTs

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
Trial design	Randomised, double-blind, active-treatment controlled, multi-centre Phase III study.	Randomised, open-label, active-treatment controlled, multi-centre Phase III study.	Randomised, open-label, multi-centre Phase II study.
Location/setting	Multi-centre study involving at 103 centres across 14 countries (Argentina, Australia, Canada, Germany, Spain, France, United Kingdom, Greece, Italy, Netherlands, Russian Federation, Sweden, Ukraine, and U.S.). The study was conducted in an out-patient hospital setting.	Multi-centre study involving 28 countries across Europe (Austria, Belgium, Czech Republic, Demark, Germany, Finland, France, Hungary, Iceland, Ireland, Italy, Netherlands, Norway, Poland, Spain, Sweden, Russian Federation, Ukraine, United Kingdom), Argentina, Australia, Brazil, Canada, New Zealand, South Korea, Swaziland, Taiwan and U.S. The study was conducted in an out-patient hospital setting.	Multi-centre study involving 16 centres across the U.S. and Australia. The study was conducted in an out-patient hospital setting.
Status of study	Ongoing. Enrolment commenced in May 2012 and closed in January 2013. Cut-off for primary analysis for PFS: 26 August 2013.[17; 109] Cut-off for final analysis of OS: 12 January 2015.[30] Follow-up is ongoing for additional survival and safety data (until all subjects have died or all subjects have at least 5 years' follow-up, whichever is earlier).	Ongoing. Enrolment commenced in June 2012 and closed in October 2013. Cut-off for interim analysis of OS (which became final): 17 April 2014.[19] Cut-off for updated analysis of OS: 13 March 2015.[20] Follow-up is ongoing for additional survival and safety data (until all subjects have died or all subjects have at least 5 years' follow-up, whichever is earlier).	Ongoing. Enrolment to Part C commenced 14 December 2010 and last subject received first dose of study drug on 07 July 2011. Initial data cut-off: 31 May 2012.[25] Follow-up for OS continues (latest data cut-off: 15 January 2015[26]) and will do until all subjects have died or all subjects have at least 5 years' follow-up, whichever is earlier.
Population	Subjects with Stage IIIc (unresectable) or Stage IV (metastatic) BRAF V600E/K mutation-positive melanoma.		Subjects with treatment-naïve metastatic BRAFV600E, V600K or V600D mutation-positive melanoma, with the exception of ≤1 previous chemotherapy regimen and/or interleukin-2 (IL-2).
Main inclusion criteria	Identical inclusion criteria: • Histologically confirmed Stage IIIC (unresectable) or Stage IV (metastatic) melanoma • Determined to be BRAF V600E/K mutation-positive*. • Measurable disease according to RECIST version 1.1.[119] • Age ≥18 years.		• Histologically confirmed metastatic BRAF V600E, V600K or V600D mutation-positive melanoma determined locally**. • Treatment-naïve for metastatic disease with the exception of ≤1

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
	• ECOG PS of 0-1. • Patients with brain metastases that had been definitively treated and stable (no increase in lesion size) for at least 12 weeks were eligible to participate • Adequate haematological, hepatic, renal and cardiac function • All prior anti-cancer treatment-related toxicities (except alopecia and laboratory Values) must be ≤ Grade 1 according to the CTCAE version 4.0 at the time of randomisation.		chemotherapy regimen and/or IL-2 regimen. • Measureable disease according to RECIST version 1.1.[119] • Age ≥18 years. • ECOG PS of 0-1. Subjects with ECOG PS 2 could be entered with approval of medical monitor • Adequate haematological, hepatic, renal and cardiac function.
Main exclusion criteria	Identical exclusion criteria: • Known ocular or primary mucosal melanoma. • Prior treatment with a BRAF inhibitor or a MEK inhibitor. • Prior systemic anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy, or investigational treatment) for Stage IIIC or Stage IV melanoma. Prior systemic treatment in the adjuvant setting is allowed. (Note: ipilimumab treatment must have ended ≥ 8 weeks prior to randomisation). • Major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, biologic therapy, or immunotherapy within 21 days prior to randomisation, or daily/ weekly chemotherapy without the potential for delayed toxicity within 14 days. • Taken an investigational drug within 28 days or 5 half-lives (minimum 14 days), whichever is shorter, prior to randomisation. • Current use of a prohibited medication (see concomitant medications below). • History of another malignancy (except subjects who have been disease-free for 3 years, or those with a history of completely resected non-melanoma skin cancer) • Any serious or unstable pre-existing medical conditions, psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures. • Known HIV, HBV or HCV infection (with the exception of chronic or cleared HBV and HCV infection which was allowed). • A history of G6PD deficiency		• Currently receiving anti-cancer therapy (chemotherapy, radiotherapy, immunotherapy, or biologic therapy) or received an investigational anti-cancer drug within 4 weeks or 5 half-lives of the first dose of study drug administration. • Prior exposure to BRAF or MEK inhibitors. • Current use of a prohibited medication (see concomitant medications below). • Current use of therapeutic warfarin; use of LMWH was permitted provided PT and PTT met entry criteria. • Known HIV, Hepatitis B or Hepatitis C infection. • Any major surgery, radiotherapy, or immunotherapy within the last 4 weeks. Limited radiotherapy within the last 2 weeks. • Evidence of brain metastases; unless all known lesions previously treated

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
	• Presence of brain metastasis (unless definitively treated with surgery or stereotactic surgery; or if present, brain lesions stable for ≥12 weeks and asymptomatic with no steroid requirement ≥4 weeks prior to randomisation; and no enzyme inducing anticonvulsant for ≥4 weeks prior to randomisation). • History or evidence of cardiovascular risk including: QTcB ≥480 msec; history or evidence of current clinically significant uncontrolled arrhythmias (except controlled atrial fibrillation); history of ACS (including MI or unstable angina) or coronary angioplasty; NYHA ≥class II heart failure; treatment-refractory hypertension; cardiac metastases; abnormal cardiac valve morphology documented by ECG; patients with intra-cardiac defibrillators or permanent pacemakers. • History or current evidence of RVO or CSR.		with surgery or stereotactic radiosurgery, and confirmed stable, and asymptomatic, and no enzyme-inducing anticonvulsants required. (cases of NED required confirmation on 2 consecutive scans prior to first dose on study). • History of pneumonitis or interstitial lung disease. • Cardiac abnormalities including: history of acute coronary syndromes; coronary angioplasty; stenting; QTc interval ≥480 msec; uncontrolled arrhythmias (except controlled atrial fibrillation); NYHA class II-IV heart failure; abnormal cardiac valve morphology; or treatment-refractory hypertension. • History of RVO or CSR, or predisposing factors. • Visible retinal pathology as assessed by ophthalmic examination. • Presence of active gastrointestinal disease or other condition that will interferesignificantly with the absorption, distribution, metabolism, or excretion of drugs.

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
Intervention and comparator	• Oral dabrafenib 150mg twice daily + trametinib 2mg once daily (n=211) • Oral dabrafenib 150mg twice daily + trametinib placebo tablets once daily (n=212) Study treatment was continued until disease progression, death, or unacceptable AE. For patients on combination treatment, if one study drug was permanently discontinued, administration of the other study drug could continue if appropriate. Patients were allowed to continue on study treatment beyond disease progression, provided specified criteria were met: (i) patient had achieved an objective response (per RECIST v1.1 ‡) or had stable disease with imaging evidence of tumour reduction lasting at least 8 weeks while on study treatment; (ii) no treatment-related adverse events of CTCAE grade 4 during the last 4 four weeks of study treatment; (iii) no signs and symptoms of clinical disease progression that decreased ECOG PS to ≥ 2; (iv) no severe clinical conditions requiring immediate surgical or radio-therapeutic intervention. After a patient has been permitted to continue on study treatment, all study procedures had to be followed as scheduled, and after each tumour assessment, the investigators had to confirm that the patient was still benefiting from study treatment. Subsequent alternative systemic anti-cancer therapy was at the discretion of investigators. Crossover from the dabrafenib monotherapy arm to the combination arm was not permitted.	• Oral dabrafenib 150mg twice daily + trametinib 2mg once daily (n=352) • Oral vemurafenib 960mg twice daily (n=352) Study treatment was continued until disease progression, death, or unacceptable AE. For patients on combination treatment, if one study drug was permanently discontinued, administration of the other study drug could continue if appropriate. Patients were allowed to continue on study treatment beyond disease progression, provided specified criteria were met: (i) patient had achieved an objective response (per RECIST v1.1 ‡) or had stable disease with imaging evidence of tumour reduction lasting at least 8 weeks while on study treatment; (ii) no treatment-related adverse events of CTCAE grade 4 during the last 4 four weeks of study treatment; (iii) no signs and symptoms of clinical disease progression that decreased ECOG PS to ≥ 2; (iv) no severe clinical conditions requiring immediate surgical or radio-therapeutic intervention. After a patient has been permitted to continue on study treatment, all study procedures had to be followed as scheduled, and after each tumour assessment, the investigators had to confirm that the patient was still benefiting from study treatment. Subsequent alternative systemic anti-cancer therapy was at the discretion of investigators. Crossover was only permitted after the Independent Data Monitoring Committee (IDMC) reviewed the results of the interim analysis (April	• Oral dabrafenib 150mg twice daily + trametinib 1mg once daily (150/1), n=54 • Oral dabrafenib 150mg twice daily + trametinib 2mg once daily (150/2), n=54 • Oral dabrafenib 150mg monotherapy twice daily, n=54 Patients who had disease progression on dabrafenib monotherapy could cross over to receive combination therapy 150/2, following confirmation by BICR.

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
		2014 cut-off) and recommended stopping the study for superior efficacy in the trametinib + dabrafenib arm (July 2014). The study protocol was subsequently amended to allow patients receiving vemurafenib to crossover to receive trametinib + dabrafenib combination therapy.	
Concomitant medication	Identical instructions regarding concomitant medications: • Subjects could receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrhoeals, and analgesics, and other care as deemed appropriate. Use of anticoagulants such as warfarin was permitted provided that INR was monitored in accordance with local institutional practice. • Certain medications were prohibited while on treatment in this study including: other anti-cancer therapies; other investigational drugs; antiretroviral drugs; herbal remedies (e.g. St. John's wort); strong inhibitors or inducers of CYP3A and CYP2C8 as they may alter dabrafenib and/or trametinib concentrations.		Subjects could receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrhoeals, analgesics, and other care, as deemed appropriate. Growth factors and bisphosphonates were allowed but could not be initiated during first 4 weeks of treatment. Certain medications were prohibited while on treatment in this study including: other anti-cancer therapies for melanoma; antiretroviral drugs; herbal remedies (e.g. St. John's Wort); therapeutic dosing of warfarin resulting in INR >1.3; strong inhibitors or inducers of CYP3A, CYP2C8, or Pgp or BCRP transporters as they may alter dabrafenib and/or trametinib metabolism.
Compliance	Identical instructions regarding compliance: • Subjects were instructed to return treatment bottles at each visit. Compliance with study treatment was assessed by querying the subject and through pill count at each visit and documented in the eCRF. A record of the number of capsules/tablets dispensed to and taken by each subject was maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates of dose modifications and/or interruptions, were also recorded in the eCRF. The investigator made every effort to bring non-compliant subjects into compliance.		When subjects were dosed at the study site, they received study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic was recorded in the source documents. The dose of study treatment and study participant identification was confirmed at the time of dosing by a member of the study site staff other than

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
			the person administering the study treatment. When subjects were not dosed at the study site, they were instructed to record the dose of study drug taken, including time and date, in the supplied GSK dosing diary.
Method of randomisation	Identical method of randomisation: • Upon completion of the required screening assessments, eligible patients were registered into the GSK interactive voice response system (RAMOS; Registration and Medication Ordering System), by the investigator or authorised site staff for stratification and central randomisation. Registered patients were assigned a unique subject number for the duration of the study. Subject number and the following information for stratification were entered into the system to obtain the blinded treatment assignment: ○ LDH (> ULN versus ≤ ULN) ○ BRAF mutation (V600E versus V600K) • Subjects in each stratum were centrally randomised using a randomisation schedule generated by the GSK Biostatistical Department, which assigned subjects in a 1:1 ratio to one or other of the interventions listed above.		Eligible patients were randomised 1:1:1 to receive one of two different dose combinations of trametinib + dabrafenib, or dabrafenib monotherapy, based on the results from the uncontrolled dose-escalation/expansion cohorts (Part B). In Part C, patients were assigned to study treatment in accordance with the randomisation schedule generated by Discovery Biometrics, using the GSK RAMOS (Registration and Medication Ordering System) interactive voice recognition system (IVRS).
Method of blinding	The study was double-blind. This was achieved by administering placebo tablets (matching trametinib tablets) to subjects randomised to the dabrafenib monotherapy arm. Treatment assignment remained blinded to GSK staff, study investigators, site staff and patients throughout the study treatment period. Only in the case of an emergency when knowledge of the study treatment was essential for the clinical management or welfare of the subject could the investigator unblind a subject's treatment assignment. Additionally, the investigator / treating physician could unblind treatment assignment for subjects who discontinued study treatment in order to determine the next appropriate anti-cancer	This was an open-label study, as it would have been complicated to construct a double-blind. This would have necessitated three types of matching placebo tablets/capsules for dabrafenib, trametinib and vemurafenib, and required patients to take multiple tablets/capsules.	This was an open-label study. Following an interim analysis based on a pre-specified protocol amendment, a Blinded Independent Central Review (BICR) was introduced to evaluate the robustness of the primary analysis, and to support Part C as a potential registration trial for the combination therapy. These analyses were primarily focused on addressing and evaluating potential sources of biases, specifically with respect to PFS.

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
	therapy.		
Primary outcomes (including scoring methods and timings of assessments)	• Investigator-assessed progression-free survival (PFS) in the entire study population ○ Defined as the interval between the date of randomisation and the earliest date of objective disease progression or death due to any cause ○ As assessed by investigators according to RECIST v1.1 criteria‡.[119] Disease assessments involving imaging (e.g. CT or MRI, skin lesion photography) were performed at baseline, week 8, and every 8 weeks through to week 56, and then every 12 weeks thereafter until determination of progressive disease, death or withdrawal of consent, whichever came first. A central review of radiological imaging data was performed by a blinded independent review committee (IRC).	• Overall survival (OS) ○ Defined as the interval between date of randomisation and date of death due to any cause. Disease assessments were conducted at baseline, every 8 weeks until week 56, and then every 12 weeks until disease progression, death, or withdrawal from the study, whichever came first.	There were multiple primary endpoints for BRF113220 Part C, including both safety and efficacy. The primary objective with respect to efficacy was to evaluate the combination relative to monotherapy with respect to co-primary endpoints of PFS, ORR, and duration of response. *Efficacy*: • Investigator-assessed progression-free survival (PFS) in the entire study population ○ Defined as the interval between the date of randomisation and the earliest date of objective disease progression or death due to any cause ○ As assessed by investigators according to RECIST v1.1 criteria‡.[119] • Overall response rate (ORR: CR + PR) ○ Defined as the percentage of patients achieving either a CR or PR (per RECIST v1.1) ‡.[119] • Duration of response (DoR) ○ Defined (based only on CR or PR) to be the date of first documented evidence of PR or CR until the earlier of date of disease progression or death due to any cause. Disease assessments were conducted at baseline and every 8 weeks, and included

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
			imaging (e.g., CT, MRI, bone scan, plain radiograph), and physical examination (as indicated for palpable/ superficial lesions). Determination of progression or response was made according to RECIST v1.1‡.[119] The primary analyses were based on investigators' assessments, with additional analyses conducted according to a blinded independent central review (BICR). Subjects whose disease responded (either CR or PR) had a confirmatory disease assessment at least 4 weeks after the date of the assessment at which response was first demonstrated. *Safety*: • Incidence of cutaneous squamous cell carcinoma (cuSCC) • Other safety measures including: ○ Incidence and severity of AEs ○ Serious adverse events (SAEs) ○ Treatment discontinuations, interruptions or dose modifications (all and due to AEs) ○ Physical, dermatological and ophthalmological examinations ○ Vital signs, ECOG PS, ECG and ECHO assessments ○ Clinical laboratory evaluations (clinical chemistry, haematology, urinalysis). All assessments were conducted at baseline. AEs and SAEs were assessed throughout

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
			the study at each visit from first dose of study treatment until 14 days after treatment discontinuation. AEs were graded according to NCI-CTCAE v4.0. Physical examinations and assessment of ECOG PS were repeated at every cycle; ECG and ECHO assessments were repeated at Week 4, and then every 12 weeks; Ophthalmologic evaluations were repeated as clinically indicated. Chemistry and haematology were assessed every 4 weeks; where applicable, laboratory data were graded using CTCAE v4.0.
Secondary outcomes (including scoring methods and timings of assessments)	*Efficacy*: • Overall survival (OS) ○ Defined as the interval between date of randomisation and date of death due to any cause. • Overall response rate (ORR: CR+PR) ○ Defined as the percentage of patients achieving either a confirmed CR or PR at any time (per RECIST criteria v1.1) ‡.[119] ○ All responses were confirmed by imaging at least 4 weeks after the first RECIST response. • Duration of response (DoR) ○ Defined as the time from the first documented evidence of CR or PR until the first documented sign of progression or	*Efficacy*: • Investigator-assessed progression-free survival (PFS) ○ Defined as the interval between the date of randomisation and the earliest date of objective disease progression or death due to any cause, as assessed by investigators according to RECIST v1.1 criteria‡.[119] • Overall response rate (ORR: CR+PR) ○ Defined as the percentage of patients achieving either a confirmed CR or PR at any time (per RECIST criteria v1.1) ‡.[119] ○ All responses were confirmed with a scan at least 4 weeks after the first RECIST response. • Duration of response (DoR) ○ Defined as the time from the first documented evidence of CR or PR until the first documented sign of progression	• Overall survival (OS) ○ Defined as the interval of time between the date of randomisation/first dose and the date of death due to any cause. • Pharmacokinetic (PK) activity ○ Blood was collected for PK analyses pre-dosing on day 15 and every 8 weeks until week 48.

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
	death due to any cause, among those subjects who achieved a confirmed CR or PR. Disease assessments were performed at baseline, every 8 weeks through to week 56 and every 12 weeks thereafter until determination of progressive disease, death or withdrawal from the study. *Health-related quality of life* (exploratory), assessed using: • EORTC-QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3) • EQ-5D (EuroQoL-5D questionnaire) Questionnaires were administered at baseline; week 8 and every 8 weeks through to week 56, and then every 12 weeks thereafter until determination of progressive disease; at the time of disease progression and 5 weeks after progression was determined. *Safety*, included: • Incidence and severity of adverse events • Serious adverse events (SAEs) • Treatment discontinuations, dose reductions or interruptions (all and due to AEs) • Clinical laboratory evaluations (clinical	or death due to any cause, among those subjects who achieved a confirmed CR or PR. Disease assessments involving imaging (e.g. CT or MRI, skin lesion photography) were performed at baseline, week 8, and every 8 weeks through to week 56, and then every 12 weeks thereafter until determination of progressive disease, death or study withdrawal. *Health-related quality of life* (exploratory), assessed using: • EORTC-QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3) • EQ-5D (EuroQoL-5D questionnaire) • Melanoma Subscale of the Functional Assessment of Cancer Therapy—Melanoma (FACT-M) questionnaire Questionnaires were administered at baseline; week 8 and every 8 weeks through to week 56, and then every 12 weeks thereafter until determination of progressive disease; at the time of disease progression and 5 weeks after progression was determined. *Safety*, included: • Incidence and severity of adverse events • Serious adverse events (SAEs) • Treatment discontinuations, dose reductions or interruptions (all and due to AEs) • Clinical laboratory evaluations (clinical	

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
	chemistry, haematology, urinalysis). • Physical, ophthalmic and dermatology examinations • Vital signs, ECOG PS, 12-Lead ECG, ECHO assessments. All safety assessments were conducted at baseline. AEs and SAEs were assessed every 4 weeks while the subject was on study treatment until 30 days after the discontinuation of study treatment. AEs were graded according to NCI-CTCAE v4.0. Physical examinations, dermatologic evaluations, assessment of ECOG PS, vital signs, and chemistry and haematology tests were repeated every 4 weeks. ECG and ECHO assessments were repeated at week 4 and every 12 weeks thereafter. An ophthalmologic evaluation was repeated at week 4 and as symptomatically warranted. *Pharmacokinetic (PK) assessments*: Blood samples were collected for PK analysis. Three blood samples were collected at week 8 (predose, 1-3 hours post dose, and 4-6 hours post dose). One blood sample was obtained at week 16 and another at week 24. Blood samples were analysed using validated methodologies to determine plasma concentrations of dabrafenib, dabrafenib metabolites (hydroxy-, carboxy- and desmethyl-dabrafenib) and trametinib.	chemistry, haematology, urinalysis). • Physical, ophthalmic and dermatology examinations • Vital signs, ECOG PS, 12-Lead ECG, ECHO assessments. All safety assessments were conducted at baseline. AEs and SAEs were assessed every 4 weeks while the subject was on study treatment until day 30 after discontinuation of study treatment. AEs were graded according to NCI-CTCAE v4.0. Physical examinations, dermatologic evaluations, assessment of ECOG PS, vital signs, and chemistry and haematology tests were repeated every 4 weeks. ECG and ECHO assessments were repeated at week 4 and every 12 weeks thereafter. An ophthalmologic evaluation was repeated at week 4 and as symptomatically warranted. *Pharmacogenetic assessments*, including: Determination of whether BRAF mutations in circulating cell-free DNA (cfDNA) correlate with mutations in the tumour tissue from which it is derived.	
Reliability or validity, and current status in clinical practice of outcome	*Overall survival (OS)*: OS is the gold standard measure of clinical benefit in oncology trials and is the primary endpoint preferred by regulatory authorities for Phase III studies.[120] It is considered the most reliable, least ambiguous and least subject to investigator bias of cancer trial endpoints; it is easy and precise to		*Progression-free survival (PFS)*: As discussed in the left-hand column, PFS measures only the effect of the study drug and is not diluted by crossover/post-

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
measures	evaluate without reliance on tumour measurements.[121] It is generally required by regulatory agencies to be a secondary endpoint where PFS is the primary endpoint.[122] However, OS is frequently confounded because of subsequent therapies administered after a study drug is discontinued or due to crossover of patients from the control arm to receive the investigational treatment upon disease progression for ethical reasons.[123] Crossover was initially prohibited in COMBI-v in order to preserve the integrity of OS as the primary endpoint. However, the results of a pre-planned interim analysis (April 2014 cut-off) dictated that the study should be stopped early for superior efficacy in the combination arm, and the protocol was amended to allow patients randomised to vemurafenib to switch to receive trametinib + dabrafenib therapy. Of the 352 patients in the vemurafenib arm, 21 (6%) had switched onto the combination as of the subsequent March 2015 data cut-off. Analyses have therefore been conducted to estimate the treatment effect of trametinib + dabrafenib compared to vemurafenib monotherapy on OS using the Rank Preserving Structural Failure Time Model (RPSFTM) and the Inverse Probability of Censoring Weights (IPCW) methodology (see section 4.4.3.2 and Table 48). Crossover was not allowed in the COMBI-d study making OS a key secondary endpoint in this study. *Progression-free survival (PFS):* PFS is widely recognised by oncologists and regulatory authorities as an important endpoint and a valid measure of clinical benefit in advanced-stage cancer trials.[122; 124] When OS is reported as primary endpoint (COMBI-v), consistency is expected as regards effects on PFS.[122] PFS is a composite endpoint that informs on both tumour response/shrinkage and disease stabilisation. As disease progression is often symptomatic and uncomfortable, an improvement in PFS is considered by medical experts to be beneficial to patients with life-threatening diseases such as late-stage melanoma, if the magnitude of the benefit is sufficient and the side-effect profile acceptable. Furthermore, PFS is a direct measure of treatment effect and is not subject to the influence of subsequent treatments that patients may receive either through crossover or post-study therapy, as OS can be.[124] A meta-analysis of a number of RCTs in metastatic melanoma showed that PFS is strongly correlated with OS.[125] A range of sensitivity analyses were performed, including an analysis to exclude studies with crossover which found a significant correlation between the treatment effects on PFS and OS. In both studies, progression was determined by the investigator using the internationally-recognised and widely used Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 [119] (‡ see footnote) based on imaging and photographic data. Sensitivity analyses are recommended for a rigorous assessment of PFS.[126; 127] Several sensitivity		study therapy making it particularly acceptable as a primary endpoint in situations where it is expected that further lines of treatment may hamper the detection of a treatment effect on OS.[124] Progression was determined by the investigator using the internationally-recognised and widely used Response Evaluation Criteria In Solid Tumours (RECIST)[119] (‡ see left-hand column) based on imaging data and photography. A number of sensitivity analyses were conducted in BRF113220 to address potential for evaluation bias and demonstrate robustness of the effect on PFS, including: investigator-assessed symptomatic PFS, investigator-assessed PFS with no censoring for extended loss to follow-up or subsequent anti-cancer therapy; PFS determined by blinded independent central review (BICR). *Overall survival (OS)*: As discussed in the left-hand column, OS is the gold standard measure of clinical benefit in Phase III RCTs of cancer therapies[124] and is generally required to be a key secondary endpoint where PFS is the primary endpoint where PFS is the primary endpoint.[122] Due to ethical requirements in clinical trials, it is necessary to allow subjects initially assigned to the control arm of a study to crossover to receive the

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18] ClinicalTrials.gov Identifier: NCT01584648	COMBI-v (MEK116513)[19; 20] ClinicalTrials.gov Identifier: NCT01597908	BRF113220 (Part C)[25; 26; 99] ClinicalTrials.gov Identifier: NCT01072175
	analyses of PFS using the ITT population were conducted in COMBI-d and COMBI-v, including: investigator-determined symptomatic progression; including all PFS events regardless of whether there was extended loss to follow-up or subsequent anti-cancer therapy prior to the event; and a Cox regression analysis using baseline prognostic factors as covariates. In COMBI-d, a blinded independent review committee (IRC), whose members were unaware of treatment assignment, reviewed the radiological findings. The progression dates determined by this review were also used to perform a sensitivity analysis of PFS. *Overall response rate (ORR)*: ORR is considered to be an appropriate and valid secondary endpoint in the Phase III evaluation of oncology drugs in many cancers, including melanoma; it provides robust supportive evidence for PFS and OS outcomes.[128] Use of the established RECIST criteria[119] ensures a high degree of uniformity in response assessments made by different reviewers. Duration of response (DoR) reflects the durability of effect of a given therapy and is considered by the oncology clinical community to be important when trying to assess the impact of a treatment on the longevity of disease control. *Health-related quality of life (HRQoL)*: The EORTC-QLQ-C30 is a self-reporting 30-item cancer specific instrument that assesses 15 domains: a global health status scale, five functional scales (physical, role, emotional, cognitive and social) and 9 symptom scales.[129] Scoring was based on published methods that transforms all scales to scores between 0 and 100.[130] Minimum clinically important differences (MCIDs) for the tool have been established and categorised as small (mean score change 5–10 points), moderate (10–20 points), and large (>20 points).[131] The EORTC QLQ-C30 has been validated in over 60 languages and shown to be highly consistent across different language/cultural groups.[129; 132] The instrument has also been found to be highly responsive to change and all scales/single items meet the standards for reliability. The EQ-5D is a standardised measure of health status that is applicable to a wide range of health conditions. It has been shown to be reliable and valid for assessing health-related QoL in cancer patients. It comprises a 5-item health status measure (index) which is used to calculate a utility value and a visual analogue rating scale (VAS/thermometer; rated 0 to 100) to rate overall health.[133] For the EQ-5D, a 0·08-point change in the utility score and a 7-point change from baseline in thermometer score are considered clinically important differences in cancer.[134] COMBI-v also included the FACT-M questionnaire which consists of the FACT-General (FACT-G) questionnaire plus the Melanoma Subscale and the Melanoma Surgery Subscale, which complement		investigational treatment upon disease progression. This ensures that all patients in the study have the opportunity of receiving the investigational treatment at some point during the study. This has the effect of confounding true survival benefit attributable to study treatment. A high proportion of patients in the dabrafenib monotherapy arm in BRF113220 crossed over to the combination 150/2 arm at disease progression; analyses were therefore conducted to examine and adjust for the impact of crossover, including the RPSFT model (see section 4.4.3.2 and Table 48).[118] *Overall response rate (ORR)*: ORR has traditionally been a primary or co-primary endpoint (as in BRF113220) in Phase II trials, and as such, has been a robust and efficient indicator of anti-tumour activity.[138; 139] Separate response analyses were performed using the investigators' and BICR's assessment of response. *Safety assessments*: A primary safety goal of BRF113220 was to identify whether combination therapy was superior to dabrafenib monotherapy in terms of occurrence of cutaneous squamous cell carcinoma (cuSCC). Subjects with cuSCC were identified using the MedDRA preferred term "non-melanoma skin lesions (squamous cell)". Safety analyses were conducted for

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	the general scale with items specific to quality of life in melanoma. High scores on all the FACT-M scales show a high quality of life. Psycho-metric testing has shown the FACT-M to be a reliable and valid instrument for patients with melanoma that can be used in clinical trials.[135] For the FACT-M Melanoma Subscale, a 2–4 point change is considered a clinically meaningful change.[136] *Safety*: AEs were coded using the industry standard dictionary for regulatory activities (MedDRA) and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) (version 4.0), a descriptive terminology that is well accepted and widely used for recording (grading) the severity of adverse events.[45] Investigators or site staff were responsible for the detection and documentation of events meeting the criteria/definition of an AE and SAE and for judging whether or not they were related to study drug. An AE or SAE was recorded for any safety assessment or laboratory test result that led to an intervention, including permanent discontinuation of study treatment and/or dose reduction/interruption. Any abnormal laboratory test results (clinical chemistry, haematology, urinalysis) or other safety assessments/events (e.g. ECG, vital sign measurements) felt to be clinically significant in the judgement of the investigator were recorded as an AE or SAE in accordance with the protocol definitions provided. Laboratory safety data were flagged high or low relative to the normal range and were graded according to the CTCAE v4.0 (where available for laboratory data). Details of adverse events (including frequency and severity) experienced by patients receiving treatments for metastatic melanoma would be recorded routinely in clinical practice. Frequent laboratory evaluations are performed in patients with metastatic melanoma in clinical practice and it is standard to compare results with reference ranges. Assessment of vital signs and physical examinations are routine clinical procedures in such patients. ECOG PS is a reliable, widely accepted and widely used method (5-point scale) of assessing the functional status and ability to self-care of cancer patients [137] and used to assess patients' performance status in clinical practice.		subjects in the randomised Phase and for crossover subjects. See left-hand column for discussion of the reliability/validity/use in current practice of the safety assessments.
Duration of follow-up	All subjects who discontinued study treatment were followed for survival every 12 weeks until death or study completion. • Median duration of follow-up (time on study) was 9 months (range 0-16) at the 26 August 2013 data cut-off.[17] • Median follow-up time at the 12 January 2015	All subjects who discontinued study treatment were followed for survival every 12 weeks until death or study completion. • Median follow-up durations were 11 months in the trametinib + dabrafenib group and 10 months in the vemurafenib group at the 17 April 2014 data cut-off.[19]	All subjects were followed for overall survival every 3 months after last doses of study drugs. • At the 31 May 2012 data cut-off, median duration of follow-up (time on study) was 14.1 months (range 10.8-17.6) months (70% PFS event rate

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	cut-off was 20 months (range 0–30) for the trametinib + dabrafenib group and 16 months (range 0–32 months) for the dabrafenib monotherapy group.[18]	• Median follow-up time at the 13 March 2015 cut-off was 19 months for the trametinib + dabrafenib arm and 15 months for vemurafenib arm.[20]	achieved). All subjects had at least 10 months follow-up.[25] • Median follow-up time at 29 March 2013 cut-off: ~24 months.[115] • Median follow-up time at 15 January 2014 cut-off: ~34 months.[117] • Median follow-up time at 15 January 2015 cut-off: ~46 months.[26]
Study funding	This study was funded, administered, and sponsored by GlaxoSmithKline	This study was funded, administered, and sponsored by GlaxoSmithKline	This study was funded, administered, and sponsored by GlaxoSmithKline

* Tumour BRAF mutation status was determined using the bioMerieux (bMx) investigational use only (IUO) THxID BRAF Assay. The assay was conducted by a central reference laboratory.
**Archived tissue was required; fresh biopsy was needed if archived tissue was not available. BRAF mutation status was determined locally using GSK BRAF mutation assay.

‡ RECIST Criteria v1.1 for evaluation of target lesions:

- Complete response (CR) – Disappearance of all target lesions
- Partial response (PR) – At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as a reference the baseline sum LD
- Progressive disease (PD) – At least a 20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
- Stable disease (SD) – Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since treatment started
- Not evaluable (NE) – Any subject who cannot be classified by one of the four preceding definitions.

ACS = acute coronary syndrome; AE = Adverse event; CNS = Central nervous system; CR = Complete response; CRF = Case record form; CSR = Central serous retinopathy; CT = Computed tomography ; CTCAE = Common Toxicity Criteria for AEs; CuSCC = Cutaneous squamous cell carcinoma; DMSO: Dimethyl sulfoxide; DoR = Duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ECG = Electrocardiogram; ECHO = Echocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D = EuroQol questionnaire; FACT-M = Functional Assessment of Cancer Therapy – Melanoma Subscale. G6PD =glucose-6-phosphate dehydrogenase; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; HIV = human immunodeficiency virus; LDH = Lactate Dehydrogenase; LMWH = low molecular weight heparin; LVEF = Left Ventricular Ejection Fraction; MI = myocardial infarction; NCI-CTCAE = National Cancer Institute-Common Toxicity Criteria for AEs; NYHA = New York Heart Association; NED = no evidence of disease; ORR = Overall response rate; OS = Overall survival; PD = Progressive disease; PFS = Progression-free survival; PK = Pharmacokinetic; PR = Partial response; RAMOS = Registration and Medication Ordering System; RECIST = Response Evaluation Criteria in Solid Tumours; QTcB = QT interval corrected for heart rate using the Bazett's formula; RVO = Retinal vein occlusion; SAE = Serious adverse event; SD = Stable disease; ULN = Upper limit of normal.

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

4.4.1. During completion of this section consider items 7a (sample size), 7b (interim analyses and stopping guidelines), 12a (statistical methods used to compare groups for primary and secondary outcomes) and 12b (methods for additional analyses, such as subgroup analyses and adjusted analyses) of the CONSORT checklist.

See Table 15 for details of the sample size calculations; statistical methods/tests used to compare groups for primary and secondary outcomes; and sub-group analyses undertaken in the COMBI-d, COMBI-v and BRF113220 studies.

The statistical methods used to adjust for confounding of OS in COMBI-v and BRF113220 due to treatment switching between the control arm and combination treatment are discussed in section 4.4.3.2.

4.4.2. For each trial listed, provide details of the trial population included in the primary analysis of the primary outcome and methods used to take account of missing data (for example, a description of the intention-to-treat analysis carried out, including censoring methods, or whether a per-protocol analysis was carried out).

See Table 15 for definitions of the analysis populations, and details of the methods used to account for missing data in the COMBI-d, COMBI-v and BRF113220 studies.

4.4.3. For each trial, provide details of the statistical tests used in the primary analysis. Also provide details of the primary hypothesis or hypotheses under consideration, the power of the trial and a description of sample size calculation, including rationale and assumptions in a table. If the outcomes were adjusted for covariates, provide the rationale. A suggested table format is presented below.

4.4.3.1 See Table 15 for details of the study hypotheses, and the rationale and assumptions behind the powering / sample size calculations used in each of the three RCTs.

Table 15: Summary of statistical analyses in the RCTs

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18; 110; 111]	COMBI-v (MEK116513)[19; 20; 113]	BRF113220 (Part C) [25; 114]
Hypothesis objective	• The primary objective of COMBI-d was to establish the superiority of trametinib + dabrafenib combination therapy over dabrafenib monotherapy with respect to PFS for subjects with advanced/metastatic BRAF V600E/K mutation-positive melanoma. • The study was designed to provide evidence with respect to efficacy using PFS to either support the null hypothesis, H0: $\lambda \geq 1$ or reject it in favour of the alternative hypothesis, HA: $\lambda < 1$, where λ is the hazard ratio (HR) between combination therapy and dabrafenib monotherapy.	• The primary objective of COMBI-v was to establish the superiority of dabrafenib + trametinib combination therapy over vemurafenib monotherapy with respect to OS for subjects with advanced/ metastatic BRAF V600E/K mutation-positive melanoma. • The study is designed to provide evidence to either support the null hypothesis, H0: $\lambda \geq 1$ or reject it in favour of the alternative hypothesis, HA: $\lambda < 1$, where λ is the hazard ratio (HR) between combination therapy and vemurafenib monotherapy, with respect to all-cause mortality.	• There were multiple primary endpoints specified for Part C, including both safety and efficacy. • The study was designed to provide evidence that the incidence rate of cuSCC experienced with the combination of trametinib + dabrafenib was 17% (absolute risk) less than that experienced with dabrafenib monotherapy. This was based on testing the following hypothesis: H0: pC - pM = 0 versus HA: pC - pM ≤ 0, where pC and pM denote the incidence rates of cuSCC experienced with the trametinib + dabrafenib combination, and dabrafenib monotherapy, respectively.
Sample size, power calculation	• The study was initially designed to have 90% power to detect a 41% reduction in the risk of progression or death (hazard ratio [HR] = 0. 59; median PFS of 5.3 and 9 months in the dabrafenib monotherapy arm and the combination arm, respectively). • Assuming a one-sided type 1 error rate of 0.025 and a randomisation ratio of 1:1, it was estimated that 340 subjects were to be enrolled in order to observe a total of 155 events (progression or death) required for the PFS analysis. With 155 events it would have been possible to detect an improvement as low as 37.7% (HR=0.726 which equates to median PFS of 7.3 and 5.3 months, respectively) with statistical significance. • The study was overenrolled by	• The overall sample size calculation was based on the OS comparison between the combination arm and vemurafenib. • Under the assumptions that PFS was exponentially distributed, 1:1 randomisation, 0.05 type I error, it was estimated that 288 deaths were needed in the final analysis to detect a HR=0.675 with 90% power (median OS times of 13.5 and 20 months in the vemurafenib arm and the combination arm, respectively, representing a 48% improvement in OS). • Given an accrual rate of 18 subjects per month over the first 6 months, and 75 subjects per month thereafter resulting in enrollment duration of approximately 13 months, an estimated total of 694 subjects (i.e. 347 subjects in each of the arms) would need to be enrolled.	• The sample size of Part C of this study was based on the demonstration of a reduction in the rate of cuSCC. With a sample size of 50 in each arm (the planned sample size for Part C), for the comparison of combination therapy (150/2) to the monotherapy, the study had 82% statistical power to detect an absolute 17% decrease in cuSCC in subjects who received combination therapy (pC=3%) compared to subjects who received dabrafenib monotherapy (pM=20%). • Fisher's exact test was utilised in these calculations, and a nominal type I error rate of 0.05 assumed. • For sensitivity analyses, with a sample size of 50 in each arm, the study had 74% statistical power to detect an absolute 16% decrease in cuSCC in subjects who received combinaton therapy (pC=4%) compared to subjects who

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18; 110; 111]	COMBI-v (MEK116513)[19; 20; 113]	BRF113220 (Part C) [25; 114]
	approximately 24% (423 patients instead of planned 340). To increase the precision of the median PFS estimate in the combination group, it was decided to perform the primary PFS analysis after 193 events had occurred which maintained the same ratio of events to patients as originally planned. As a result, the overall power increased from 90% to 95%. • A pre-specified interim analysis of OS was planned at the time of the primary PFS analysis. PFS was significant at a level of 0·05 but OS was not significant at the pre-specified level of 0·00028. • The final OS analysis was performed when 70% of the 340 planned subjects (220 events) had died or been lost to follow-up (anticipating a 5% loss to follow-up). When the study was designed, it was estimated that 220 events would provide roughly 80% power to detect an HR of 0·675. • A Lan and DeMets[140] alpha-spending function, with O'Brien and Fleming[141] like boundaries for efficacy was used to control the type I error rate, with a global alpha level of 5%. The threshold for significance was a two-sided p-value of less than 0·0496.	• A pre-planned interim analysis for OS was planned for when 70% (i.e. n=220) of the total number of deaths (N=288) required for the final analysis had been observed. It was estimated that this would occur at approximately 17 months after the start of the study. • Owing to the inherent lag in data entry, the actual number of deaths at the time of the cut-off for the interim analysis (17 April 2014) was 222. The study protocol specified that efficacy boundaries would be adjusted based on the actual number of deaths at the interim analysis. • The adjusted stopping boundaries (stop for efficacy at interim if two-sided p-value is <0.0214, and stop for futility at interim if two-sided p-value is >0.2210) were utilised by the Independent Data Monitoring Committee (IDMC) to review the interim OS data on 09 July 2014. The IDMC recommended stopping the study for efficacy. As such, the interim OS summary is considered to be the final comparative analysis of OS. • An updated analysis based on 349 death events was conducted with a data cut-off of 13 March 2015.	received dabrafenib monotherapy (pM=20%).
Analysis populations	• The *Intent-to-Treat (ITT)* population comprised all randomised subjects regardless of whether or not treatment was administered. This population was based on the treatment to which the subject was randomised and was the	• The *ITT population* comprised all randomised subjects regardless of whether or not treatment was administered. This population was based on the treatment to which the subject was randomised and was the primary population for efficacy analyses.	• The *Intent-to-Treat (ITT)* population comprised all randomised subjects regardless of whether or not treatment was administered. This population was based on the treatment to which the subject was randomised and was the primary population for the analysis of efficacy data in

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18; 110; 111]	COMBI-v (MEK116513)[19; 20; 113]	BRF113220 (Part C) [25; 114]
	primary population for efficacy analyses. • The *Safety population* comprised all randomised subjects who received at least one dose of study medication and was based on the actual treatment received if this differed from that to which the subject was randomised. • The *PK population* comprised all subjects included in the Safety population for whom at least 1 PK sample was obtained and analysed.	• The *Safety population* comprised all randomised subjects who received at least one dose of study medication and was based on the actual treatment received if this differs from that to which the subject was randomised. • The *cfDNA Population* consisted of all subjects from the ITT population for whom samples for cfDNA have been obtained and analysed.	Part C. • The *All Treated Population* consisted of all subjects that received at least one dose of investigational product. Safety and clinical activity data were evaluated based on this population. • The *PK Population* consisted of those subjects in All Treated Population and for whom a PK sample was obtained and analysed.
Statistical analyses/ methods	*Efficacy analyses:* • PFS and OS were estimated using the Kaplan Meier method and treatment comparisons were be made using a stratified log-rank test (based on the two stratification factors). The Pike estimator[142] of the treatment HR along with the 95% confidence intervals (CIs) are provided. In addition, for each treatment group, the Kaplan-Meier estimates for the median, the first and third quartiles are presented, along with approximate 95% CIs. • Sensitivity analyses of PFS were conducted in order to confirm the results of the primary analysis, including: PFS determined by a blinded independent review committee; PFS based on symptomatic progression determined by the investigator; considering start of new anti-cancer therapy as an event; and considering radiological progression after extended loss to follow-up or start of new anti-cancer therapy as an event.	*Efficacy analyses:* • OS and PFS were estimated using the Kaplan Meier method and treatment comparisons were made using a stratified log-rank test (based on the two stratification factors). The Pike estimator[142] of the treatment HR along with the 95% confidence intervals (CIs) are provided. In addition, for each treatment group, the Kaplan-Meier estimates for the median, the first and third quartiles are presented, along with approximate 95% CIs. • Sensitivity analyses of PFS were performed, including: PFS based on symptomatic progression determined by the investigator; considering start of new anti-cancer therapy as an event; considering radiological progression after extended loss to follow-up or start of new anti-cancer therapy as an event; using derived responses from investigator lesion assessments. • ORR was calculated based on number/ percentage of subjects in each treatment arm attaining either a confirmed best response of CR or PR. A bone scan was not	*Efficacy analyses*: • PFS and OS were summarised using Kaplan-Meier estimates. For each treatment group, the Kaplan-Meier estimates for median PFS and OS and the first and third quartiles are presented, along with 95% CIs. CIs for quartiles were estimated using the Brookmeyer-Crowley method. For the PFS and OS comparison of each combination arm with the monotherapy arm, p-values based on two-sided log rank test were calculated; the Pike estimate[142] of treatment HRs are provided, together with a 95% CI. • ORR was calculated based on number/ percentage of subjects in each treatment arm attaining a best response of CR or PR (per RECIST v1.1). Per protocol, to be assigned a status of PR or CR as best confirmed response, a confirmatory disease assessment had to be performed ≥28 days after the criteria for response were first met. ORR for best unconfirmed response and best confirmed response were summarised separately. Exact 95% CI for ORR were calculated. The ORR of each combination arm was compared to the

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18; 110; 111]	COMBI-v (MEK116513)[19; 20; 113]	BRF113220 (Part C) [25; 114]
	• An updated analysis of PFS that was not in the original analysis plan was carried out at the time of the final OS analysis. The updated analyses were the same as those in the primary PFS analysis with the exception that the independent review had been discontinued, so only investigator assessed results were updated. • ORR was calculated based on number/percentage of subjects in each treatment arm attaining a confirmed best response of CR or PR (per RECIST v1.1) at any time; best response was determined pragmatically by GSK based on investigators' assessment of response at each time point. The difference in response rates between treatment arms was calculated along with corresponding 95% CI. A chi-square test was used to test for association between treatment arm and response. • Duration of response (DoR) was summarised for subjects with a confirmed CR or PR and the median was calculated using Kaplan-Meier estimates. • Adjustments for multiplicity were not undertaken for analyses than were not pre-planned. *Safety analyses*: • No formal tests for comparison were provided for the safety analyses. • Adverse events (AEs) were coded using standard MedDRA terms and grouped by organ class. AEs were graded by the	required to confirm response. Per protocol stable disease must have been at the 8-week assessment or later in order to qualify for best response. The 95% CI for the response rates in each treatment arm was calculated and response rates were compared between treatment arms using a chi-square test. Additionally, the difference between response rates in the treatment arms and the associated CI for that difference were calculated. • DoR was summarised for subjects with a confirmed CR or PR and the median was calculated using Kaplan-Meier estimates. • Adjustments for multiplicity were not undertaken for analyses that were not pre-planned. *Safety analyses*: • No formal tests for comparison were planned for the safety analyses. • Adverse events (AEs) were coded using standard MedDRA terms and grouped by organ class. AEs were graded by the	monotherapy arm using exact test; 95% CIs for the differences in ORRs were calculated using the exact method. • The duration of response (DoR) comparison of each combination arm with the monotherapy arm, p-value based on two-sided log rank test was calculated; the Pike estimate[142] of treatment hazard ratios (HR) are provided, together with a 95% CI. • PFS and ORR were analysed separately for the randomised phase (ITT population) and for subjects who crossed over. When calculating OS, all deaths following crossover were included. *Safety analyses*: • AEs were graded according to the NCI CTCAE v4.0. A summary of all AEs by maximum toxicity grade was provided. Separate summaries were also provided for all AEs, drug-related AEs, serious AEs, and AEs leading to treatment discontinuation. • AEs of special interest were also summarised (including cuSCC, pyrexia, cardiac-related events, hepatic events, ocular events, skin-related toxicities). • Where applicable, laboratory data were graded using CTCAE v4.0. A summary of grade increases comparing the baseline grade to the worst-case post-dose grade were provided. Any increase in grade was summarised along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Summaries of worst-case chemistry and haematology change from baseline with respect to the normal range were provided for non-graded laboratory tests. Additional summaries of Liver Function

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18; 110; 111]	COMBI-v (MEK116513)[19; 20; 113]	BRF113220 (Part C) [25; 114]
	investigator according to the NCI CTCAE, version 4.0. Separate summaries were provided for all AEs, drug-related AEs, SAEs and AEs leading to treatment discontinuation. If the AE was listed in the NCI CTCAE (version 4.0) table, the maximum Grade was provided. A number of AEs of special interest (including cuSCC and other proliferative diseases) were also summarised. • Clinical chemistry and haematology data were summarised according to NCI CTCAE grade (version 4.0). The maximum toxicity grade of a laboratory parameter for a subject was the worst grade post-baseline after the first dose of study treatment over the treatment period. Any grade increases and specific increases to Grade 1, Grade 2, Grade 3, and Grade 4 were summarised. The proportion of values lying outside the reference range were presented for laboratory tests that are not graded because there are no associated NCI CTCAE criteria. *Health-related quality of life (HRQoL) analyses*:[28] • HRQoL analyses were based on the ITT population. • Baseline scores (defined as HRQoL assessment before first dose) were reported with standard descriptive statistics. Changes in scores from baseline at each assessment time point were summarised for global health and	investigator according to the NCI CTCAE, version 4.0. Separate summaries were provided for all AEs, drug-related AEs, SAEs and AEs leading to treatment discontinuation. If the AE was listed in the NCI CTCAE (version 4.0) table, the maximum Grade was provided. A number of AEs of special interest (including cuSCC and other proliferative diseases) were also summarised. • Clinical chemistry and haematology data were summarised according to NCI CTCAE grade (version 4.0). The maximum toxicity grade of a laboratory parameter for a subject was the worst grade post-baseline after the first dose of study treatment over the treatment period. Any grade increases and specific increases to Grade 1, Grade 2, Grade 3, and Grade 4 were summarised. The proportion of values lying outside the reference range were presented for laboratory tests that are not graded because there are no associated NCI CTCAE criteria. *Health-related quality of life (HRQoL) analyses*:[29] • HRQoL analyses were based on the ITT population. • Changes in score from baseline at each assessment time point were summarised for: scores for global health and for each functional and symptom scale or single item of EORTC-QLQ-C30; utility and VAS scores of EQ-5D; and melanoma subscale score of FACT-M.	Tests were provided to evaluate the potential for liver toxicity. • Safety analyses were handled separately for the randomised and crossover phases. No adjustments for multiple comparisons were made in either the analysis of efficacy or cuSCC. *Pharmacokinetic analyses*: • Pre-dose concentration-time data from Part C were listed for each subject and summarised by descriptive statistics at each visit and by treatment group. Concentration data obtained in Part C were combined with Parts A, B and D, and analysed using a population approach.

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18; 110; 111]	COMBI-v (MEK116513)[19; 20; 113]	BRF113220 (Part C) [25; 114]
	for each functional and symptom scale or single item of the EORTC QLQ-C30 questionnaire. • Analysis of covariance—adjusted for baseline score using mixed-model repeated measures with time, treatment and treatment by time interaction as fixed effects—was carried out to assess differences between arms for global health and all functional and symptom dimension scores. Time was treated as the repeated variable. Unstructured covariance matrices were used for these analyses. • For the EQ-5D, changes in scores from baseline at each assessment time point were summarised for the utility and VAS scores. Changes in the mean scores over time were assessed for differences between treatment arms using mixed-model repeated measures analyses. • The study was not powered for the HRQoL endpoints and there was no HRQoL hypothesis, therefore all HRQoL results should be considered exploratory. *Pharmacokinetic analyses*: • Details of the pharmacokinetic and pharmacodynamic analyses can be found in the study protocol.	• Changes in the mean scores over time were analysed with a repeated measures ANCOVA by use of baseline score as covariate with time, treatment, baseline score, baseline score by time interaction, and treatment by time interaction as fixed effects for all 15 domain scores of the EORTC QLQ-C30, the thermometer and utility scores of the EQ-5D, and the FACT-M melanoma subscale score. Time was treated as the repeated variable within subject. An unstructured covariance matrix was used and a mixed effects model with analyses by Proc Mixed of SAS, version 9.2. Maximum likelihood was restricted to estimate the parameters of the model and unstructured variance–covariance matrices in the repeated measures model. • Adjusted means and associated standard error of the changes from baseline are reported for each assessment time for which adequate data were available. P-values based on the two-sided Wald test are provided. • The study was not powered for the HRQoLendpoints and there was no HRQoL hypothesis, therefore all HRQoL results should be considered exploratory. *Pharmacogenetic analyses*: • Details of the pharmacogenetics analyses can be found in the study protocol.	
Data management, patient withdrawals	*Treatment discontinuation*: • Subjects received study treatment until disease progression, death or unacceptable toxicity. . Subjects could	• The processes for data management and handling treatment discontinuation / patient withdrawals / missing data were as for the COMBI-D study (see left-hand column).	• The processes for data management and handling treatment discontinuation / patient withdrawals / missing data were as for the COMBI-D study (see left-hand column).

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18; 110; 111]	COMBI-v (MEK116513)[19; 20; 113]	BRF113220 (Part C) [25; 114]
	continue on study treatment beyond disease progression in certain circumstances as detailed in Table 14. Subjects could also withdraw from the study for other reasons. All subjects who withdrew were included in analyses up to the time of withdrawal, regardless of treatment duration. All subjects who permanently discontinued study treatment without disease progression were followed until progression, start of new anti-cancer therapy, or death. Subjects are still being followed-up until death. Collection of follow-up data will continue until all of the enrolled subjects have died or been lost to follow-up, or all subjects in follow-up have had at least 5 years of follow-up (from randomisation), whichever is earlier, at which point the study will close to further follow-up. *Withdrawals*: • A subject was considered to have withdrawn from the study if the subject had not died and was lost to follow-up, had withdrawn consent, was no longer being followed at the investigator's discretion, or if the study is closed or terminated. A subject is considered to have completed the study if the subject dies during the study treatment or follow-up period. *Missing data*: • All available time-to-event data were analysed using suitable statistical methods; patients with shorter treatment		

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18; 110; 111]	COMBI-v (MEK116513)[19; 20; 113]	BRF113220 (Part C) [25; 114]
	and follow-up due to the natural history of their disease or medical necessities of the treatment of their disease were not be considered to have missing time-to-event data. There was no imputation for missing data. Subjects with unknown or missing best response data were assumed to be non-responders, and included in the denominator when calculating percentages. *Censoring*: • PFS: Subjects with a progression event after an extended period or who were lost to follow-up were censored at the date of the last adequate assessment prior to the event (even if subsequent information was available regarding progression or death). Additionally subjects who started a new anticancer therapy prior to progression were censored at the last adequate assessment prior to the start of new therapy. Subjects who had not progressed or died at the time of analysis were censored at the last adequate assessment. • OS: Subjects who died after an extended period without adequate assessment were censored at their date of last adequate assessment prior to death. For those believed to be still alive at the time of the analysis, censoring was performed using the date of last known contact.		
Subgroup analyses	Subjects were stratified for two baseline factors:	Subjects were stratified for two baseline factors:	A planned stepwise Cox regression analysis explored various pre-determined factors as covariates:

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18; 110; 111]	COMBI-v (MEK116513)[19; 20; 113]	BRF113220 (Part C) [25; 114]
	• BRAF V600 mutation (V600E or V600K) • Baseline LDH levels (≤ULN or >ULN) Additional pre-determined factors considered to be important prognostic determinants in melanoma[5; 57; 143] were explored in a stepwise Cox regression model: • Age (continuous) • Gender (male or female) • Baseline ECOG performance status (0 or 1), • Baseline disease stage (IIIcM0/IVM1a/IVM1b or IVM1c) • Visceral disease at baseline (yes or. no) • Number of disease sites at baseline (<3 or. ≥3). Pre-planned univariate subgroup analyses explored for the PFS and OS endpoints were: • BRAF V600 mutation (V600E or V600K) • Age (<65 years or ≥65 years) • Gender (male or female).[17] Additional univariate subgroup analyses of PFS and OS were undertaken *post hoc* based on the results of the Cox model including: • Baseline LDH levels (≤ULN or >ULN) • Baseline ECOG performance status (0 or ≥1) • Disease stage at baseline (IIIcM0, IVM1a, IVM1b or IVM1c) • Presence of visceral disease at baseline (absent or present) • Number of disease sites at baseline (<3 or ≥3). • Prior immunotherapy (yes or no). Mutation status (pre-specified) and baseline	• BRAF V600 mutation (V600E or V600K) • Baseline LDH levels (≤ULN or >ULN) A stepwise stratified Cox regression model analysed the effect of various pre-determined prognostic factors: • Gender (male or female) • Baseline ECOG performance status (0 or 1), • Baseline disease stage (IIIcM0/IVM1a/IVM1b or IVM1c) • Number of disease sites at baseline (<3 or. ≥3). Univariate subgroup analyses of PFS and OS were undertaken in a similar way to the COMBI-d study and included: • BRAF V600 mutation (V600E or V600K) • Age (<65 years or ≥65 years) • Gender (male or female) • Baseline LDH levels (≤ULN or >ULN) • Baseline ECOG performance status (0 or ≥1) • Disease stage at baseline (IIIcM0, IVM1a, IVM1b or IVM1c) • Presence of visceral disease at baseline (absent or present) • Number of disease sites at baseline (<3 or ≥3) • Prior immunotherapy (yes or no). Mutation status, baseline LDH level and gender	• Age (<65 years or ≥65 years) • Gender (male or female) • BRAF V600 mutation (V600E or V600K) • Baseline LDH levels (≤ULN or >ULN) • Disease stage at baseline (IIIcM0, IVM1a, IVM1b or IVM1c) • Brain metastases at baseline (present or absent). Pre-planned univariate subgroup analyses explored for some of the efficacy endpoints were: • Age (<65 years or ≥65 years) • Gender (male or female) • BRAF V600 mutation (V600E or V600K). Additional univariate subgroup analyses were considered based on the results of Cox model. Subgroup analyses of some safety data were undertaken by gender (male vs. female) and age (< 65 years vs. ≥65 years; <75 years vs. ≥75 years.

Trial no. (acronym)	COMBI-d (MEK115306)[17; 18; 110; 111]	COMBI-v (MEK116513)[19; 20; 113]	BRF113220 (Part C) [25; 114]
	LDH level (*post hoc*) were explored in the subgroup analysis of ORR. The following subgroups were explored in the analysis of key safety data, where the subgroups were large enough to result in meaningful analyses: gender (male vs. female) and age (≥65 vs. <65 years, and ≥ 75 vs. <75 years). The subgroup analyses were performed with the use of an unstratified log-rank test to compare treatment arms within each subgroup. Kaplan-Meier quartile estimates were created for each treatment arm within the subgroup categories, and HRs were also calculated within each subgroup category. No tests for interaction have been performed and p-values are not available for any subgroup comparisons.[17]	were explored in the subgroup analysis of ORR. Subgroup analyses of some safety data were undertaken by gender (male vs. female) and age (≥65 vs. <65 years, and ≥ 75 vs. <75 years). The subgroup analyses were performed with the use of an unstratified log-rank test to compare treatment arms within each subgroup. Kaplan-Meier quartile estimates were created for each treatment arm within the subgroup categories, and HRs were also calculated within each subgroup category. No tests for interaction have been performed and p-values are not available for any subgroup comparisons.	

ANCOVA = Analysis of Covariance; AE = Adverse event; CR = Complete response; DoR = Duration of response; ECOG PS = European Cooperative Oncology Group Performance Status; EORTC = European Organization for Research and Treatment of Cancer; FACT-M = Functional Assessment of Cancer Therapy – Melanoma Subscale; HR = Hazard ratio; HRQoL = Health-related quality of life; ITT = Intent-to-Treat; LDH = Lactate dehydrogenase; NCI-CTCAE = National Cancer Institute-Common Toxicity Criteria for AEs; ORR = Overall response rate; OS = Overall survival; QLQ = Quality of Life Questionnaire; PFS = Progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = Serious Adverse Event

4.4.3.2 Statistical methodology to adjust for confounding due to treatment switching in COMBI-v and BRF113220

In BRF113220 (Part C), patients randomised to the dabrafenib monotherapy arm were permitted to switch to receive the combination of the trametinib + dabrafenib, upon independently confirmed disease progression. In the COMBI-v study, crossover was prohibited until the IDMC recommended stopping the study early for efficacy having reviewed the findings from a pre-planned interim analysis (April 2014 cut-off). This led to the study protocol being amended (August 2014) to allow patients in the vemurafenib group to cross over to combination therapy.[20] Data collection continued and a subsequent analysis of OS (March 2015 cut-off) has therefore been impacted by treatment switching. The COMBI-d study did not permit patients to crossover from the dabrafenib monotherapy to receive combination therapy in order to preserve the integrity of OS as a key secondary endpoint.

Table 16 presents the proportion of patients who had crossed over at the different data points within the COMBI-v and BRF113220 studies.

Table 16: Level of patient crossover in COMBI-v and BRF113220

	COMBI-v		**BRF113220 (Part C) (150/2 arm)**	
Data cut-off (date)	**April 2014**	**March 2015**	**May 2012**	**January 2015**
Number (%) control group crossing over	0 / 352 (0%)	21* / 352 (6%)	43 / 54 (80%)	45 / 54 (83%)

* Only 5 of the 21 patients experienced disease progression.

Where crossover occurs, ITT analyses may underestimate the incremental benefit of treatment on OS because they do not account for the fact that patients in the control arm are likely to have performed better having crossed over to receive the investigational treatment than they may have done had they not been afforded this opportunity. The optimal method to adjust for the confounding effect of crossover in survival analyses in RCTs remains an area of academic debate and all approaches have their strengths and weaknesses.

Naive methods such as censoring patients at the time they crossover or excluding them from the analysis are highly prone to selection bias because treatment crossover is likely to be associated with prognosis and the randomisation balance between groups is broken.[144] These methods are explicitly not recommended by NICE[145] but have been applied to the COMBI-v and BRF113220 datasets for completeness and comparison; however, their results should not be relied upon for clinical or economic analyses (see Table 48).

For this reason, more complex methods have emerged that attempt to adjust more effectively for the effect of treatment switching, including: the Rank Preserving Structural Failure Time Model (RPSFTM), the Iterative Parameter Estimation (IPE) algorithm, and Inverse Probability of Censoring Weights (IPCW). These methodologies have been applied in several recent NICE appraisals, including the assessments of dabrafenib and vemurafenib as monotherapies[81; 82] – the comparators in this decision problem. Each of these methods makes important assumptions and has associated limitations which should be taken into account when considering the optimal approach for a specific trial set.

An extensive assessment of which methods would be most appropriate for the COMBI-v and BRF113220 data sets was undertaken by the School of Health and Related Research (ScHARR) in Sheffield and full details are available in the technical report provided in the reference folder accompanying this submission.[27; 118] ScHARR chose to apply the RPSFTM and the IPCW methodology to the COMBI-v data set[27], and the RPSTFM and IPE algorithm to the BRF113220 data set[118] for reasons discussed below.

(i) Rank Preserving Structural Failure Time Model (RPSFTM)

The RPSFTM uses a counterfactual framework to estimate survival times – that is, the survival times that would have been observed in the absence of treatment switching – based upon the randomisation of the trial. The standard one-parameter version of the method is reliant upon the 'common treatment effect' assumption – i.e. the treatment effect received by switching patients is equal (relative to the time it is taken for) to the treatment effect received by patients initially randomised to the intervention group. Additionally, RPSFTM assumes that randomisation must have balanced the treatment groups so there are no differences between them, apart from the treatment allocated.[146] When these key assumptions are satisfied, RPSFTM has been shown to produce very low levels of bias.[147; 148]

RPSFTM method

The standard one-parameter RPSFTM splits the observed event time (Ti) for each patient into two: time spent on the control treatment (TAi), and time spent on the intervention treatment (TBi). For patients who are randomised to the intervention treatment, and who do not switch onto the control treatment (i.e. when compliance is full in the treatment group), TAi is equal to zero. For patients randomised to the control group who do not switch onto the intervention (i.e. compliance is full in the control group) TBi is equal to zero. However, for patients who switch treatments (for whom compliance is imperfect) both TAi and TBi will be greater than zero. The standard one-parameter RPSFTM method relates Ti to the counterfactual event time (Ui) with the following causal model:
$Ui = T_{Ai} + e^{\psi 0} T_{Bi}$

Step 1 involves estimating the value of ψ using g-estimation. A log-rank test can be used to determine the value of ψ for which counterfactual survival times are independent of randomised groups (for which the test (z) statistic equals zero).

Step 2 involves estimating the HR for OS for randomisation to the intervention group vs. randomisation to control therapy with no switching to the intervention therapy, by fitting a Cox proportional hazards regression model to the observed intervention treatment survival times and re-censored adjusted survival times for patients on control therapy based on the estimate of ψ. Confidence intervals are estimated for the RPSFTM adjusted HRs using a test-based procedure that retains the p-value from the unadjusted ITT analysis.

The randomisation assumption should be reasonable in the context of an RCT, but may be called into question if sample sizes are particularly small, such as in the case of BRF113220. The 'common treatment assumption' may be problematic where switching is only permitted after disease progression, such that the capacity of switchers to benefit could be lower than patients initially randomised to the intervention group, because switchers receive the treatment at a more advanced stage of their disease. However, in the COMBI-v trial

treatment switching was not related to disease progression; only 5 of the 21 switching patients had experienced disease progression.

Re-censoring represents an additional limitation of the RPSFTM method since it involves 'throwing away' information; the larger the treatment effect, the more information that is discarded. The re-censoring rule applied to the COMBI-v trial differs from that applied to the BRF113220 trial, due to circumstances when switching was permitted. In BRF113220, switching was permitted after disease progression, whereas in the COMBI-v, switching was only permitted after the protocol amendment, regardless of whether patients had progressed or not. Re-censoring seeks to break the dependence between censoring time and the treatment received. For control group patients who did not switch onto a beneficial new treatment and died close to their administrative censoring time, the event may not have been observed had they received the new treatment; these patients therefore have their survival times re-censored and their events are no longer observed.[149] In BRF113220, the dependence between censoring time and treatment was assumed to be present throughout the trial. In COMBI-v, patients were not permitted to switch treatments until 07 August 2014, so re-censoring was only necessary from this date to the 13 March 2015 cut-off, and thus, did not result in a large loss of information.

If treatment effect changes over time, re-censoring can add to any bias associated with RPSFTM – e.g. if the treatment effect falls over time, recensoring may lead to an over-estimation of the true treatment effect. Given there was no evidence of a changing treatment effect on OS over time, RPSFTM analyses which included re-censoring were considered preferable to those that excluded recensoring.[118]

A key advantage of the RPSFTM method is that it produces a randomisation-based effect estimator (RBEE).[149] By design, its significance level remains the same as that of the ITT analysis and the p-value is retained; however, the confidence intervals around the HR point estimate may widen.

(ii) Iterative Parameter Estimation (IPE)

The IPE is an extension of the RPSFTM using parametric methods. This uses the same accelerated failure time model but fits a parametric failure time model (e.g. Weibull, log logistic, lognormal) to the original, unadjusted ITT data to obtain an initial estimate of ψ. The observed failure times of switching patients are then re-estimated using the counterfactual survival time model presented in the equation in (i) above, and the treatment groups are compared again using the parametric model to give an updated estimate of ψ. The process of re-estimating the observed survival times of crossover patients is repeated in an iterative process until the new estimate for e^{ψ} is very close to the previous estimate at which point the process is said to have converged. As with the RPSFT method, the significance level remains the same as that associated with the ITT analysis. The IPE method produces very low levels of bias when the assumptions made by the method (in particular, the "common treatment effect" assumption) hold.[150; 144; 151] Morden[150] and Latimer[144] found that the method's performance was very similar to the RPSFT, which is to be expected as the methods are similar other than in their estimation procedure.

For both the RPSFTM and IPE methods, two sets of analyses were conducted testing different assumptions regarding the durability of the treatment effect: "Treatment group"

analyses in which it was assumed that the treatment effect is maintained until death regardless of treatment duration, and "On Treatment" analyses in which it was assumed that the treatment effect disappears upon treatment discontinuation. The RPSFTM 'treatment group' approach is generally subject to less re-censoring than the RPSFTM 'on treatment' method.

Alternative applications of the RPSFTM and IPE methods

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

- *On treatment analysis*: In this approach, crossover is accounted for not only from the control group to the intervention treatment, but also from intervention treatment to the control group. This results in a "causal" treatment effect being estimated for the intervention treatment – i.e. the effect while on treatment. Essentially this provides an estimate of the treatment effect of full treatment (with no discontinuation) compared to no treatment and it assumes that the treatment effect is lost as soon as treatment is discontinued.
- *Treatment group analysis*: This analysis assumes that there is no crossover from the intervention treatment onto the control treatment and once treatment has begun the patient remains in the "treated" group. This approach estimates the average effect of being randomised to the intervention group compared to the control group over the entire observed lifetimes of patients – it does not require that the treatment effect stops upon treatment discontinuation.

(iii) Inverse Probability of Censoring Weighting (IPCW) analysis

The IPCW method is not reliant upon the 'common treatment' effect assumption. It censors patients at the point of treatment switch and then weights remaining observations based upon baseline and time-dependent covariates, in order to adjust for any selection bias caused by the switching-related censoring. This method is reliant upon the 'no unmeasured confounders' assumption, which means that data must be available on all baseline and time-dependent patient characteristics that influence the probability of treatment switch and the probability of death. Essentially, patients in the control group who do not switch (and prior to the point of switch) form a 'pseudo' control group population. Owing to this, and the reliance of the method on observational data, the IPCW method is particularly prone to error when sample sizes are small – especially when few control group patients do not switch (i.e. a high proportion of control patients do switch).[152] This was the case in the BRF113220 study and consequently it was decided not to undertake the IPCW method. However, in the COMBI-v trial, sample sizes were substantial and the number of non-switchers was high; nevertheless, bias may still be introduced through a lack of available time-dependent data, resulting from cessation of data collection for some covariates after the interim analysis stage.

Summary

For reasons discussed (including samples sizes, levels and timing of crossover), the RPSFTM 'treatment group' approach was deemed the most appropriate method to adjust the COMBI-v and BRF113220 OS data to produce an estimate of treatment effect that would have been observed in the absence of treatment switching.[27; 118] This approach has therefore been selected as the adjustment method for our economic analyses that use the COMBI-v

OS data (see Section 5). Results from this and all the other OS adjustment analyses are provided in Table 48.

Full technical details regarding the application of these methods to the COMBI-v and BRF113220 data sets and the results obtained can be found in the technical reports accompanying this submission.[27; 118]

4.5. Participant flow in the relevant randomised controlled trials

4.5.1. Provide details of the numbers of participants who were eligible to enter the trials. Include the number of participants randomised and allocated to each treatment. Provide details of and the rationale for participants who crossed over treatment groups, were lost to follow-up or withdrew from the RCT. Provide a CONSORT diagram showing the flow of participants through each stage of each of the trials.

Patient disposition in COMBI-d

A total of 423 patients were randomised 1:1 to study treatment (trametinib + dabrafenib, N=211; dabrafenib + placebo N=212). At the time of the latest data cut-off (12 January 2015), 31% of patients in the combination arm and 17% in the dabrafenib monotherapy arm remained on study treatment (Table 18), and 44% and 36% of patients, respectively, were still ongoing in the study (Table 17). This information is also presented as a CONSORT flow diagram in Figure 7.[17; 18; 110; 111]

Table 17: Summary of subject disposition in COMBI-d (ITT population)

	13 August 2013 cut-off[17; 110]		12 January 2015 cut-off[18; 111]	
	Trametinib + dabrafenib N=211	Dabrafenib monotherapy N=212	Trametinib + dabrafenib N=211	Dabrafenib monotherapy N=212
Subject status, n (%)				
Died	40 (19)	55 (26)	98 (46)	120 (57)
Ongoing	154 (73)	147 (69)	93 (44)	76 (36)
Withdrawn from study[a]	17 (8)	10 (5)	20 (9)	16 (8)
Primary reason for early withdrawal, n (%)				
Lost to follow-up	4 (2)	3 (1)	6 (3)	7 (3)
Investigator decision	2[b] (<1)	2[c] (<1)	2[b] (<1)	2[c] (<1)
Withdrew consent	11 (5)	5 (2)	12 (6)	7 (3)

a. Four subjects who withdrew from the study (1 in the combination therapy arm and 3 in the dabrafenib monotherapy arm) subsequently had date of death reported. These subjects are only counted under withdrawn in this table.
b. 1 subject did not take study treatment; 1 subject was randomised in error.
c. 1 subject failed screening and was randomised in error; 1 subject was not compliant.

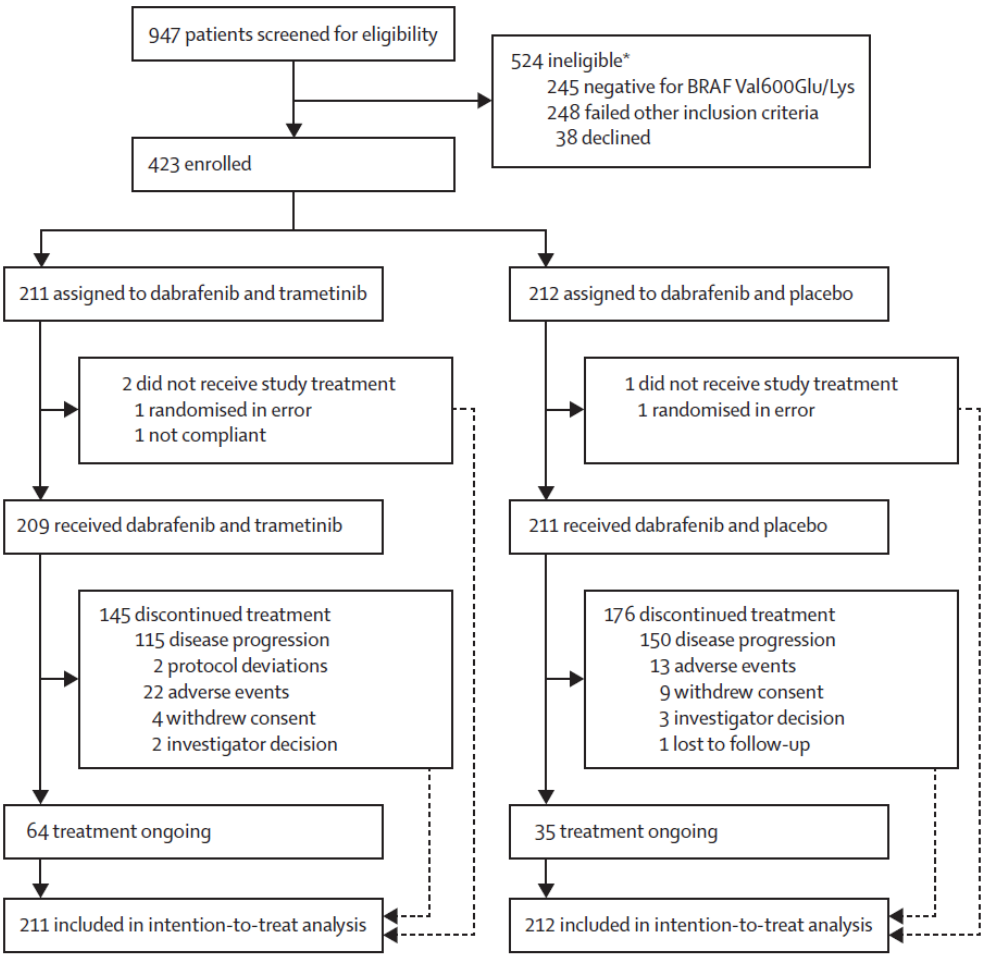
Table 18: Treatment status in COMBI-d (ITT population)

	13 August 2013 cut-off[17; 110]			12 January 2015 cut-off[18; 111]		
	Trametinib + dabrafenib N=211		Dabrafenib mono therapy N=212	Trametinib + dabrafenib N=211		Dabrafenib mono therapy N=212
	Dabrafenib	Trametinib		Dabrafenib	Trametinib	
Subject status, n (%)						
Ongoing	110 (53)	111 (53)	90 (43)	63 (30)	64 (31)	35 (17)
Discontinued	99 (47)	98 (47)	121 (57)	146 (70)	145 (69)	176 (83)
Primary reason for discontinuation[a], n (%)						
Disease progression	75 (36)	74 (35)	102 (48)	116 (56)	115 (55)	150 (71)

Adverse event	18 (9)	17 (8)	10 (5)	23 (11)	22 (11)	13 (6)
Protocol deviation	1[b] (<1)	1[b] (<1)	0	2[e](<1)	2[e] (<1)	0
Lost to follow	0	0	1 (<1)	0	0	1 (<1)
Investigator decision	2[c] (<1)	2[c] (<1)	1[d] (<1)	2[c] (<1)	2[c] (<1)	3[f] (1)
Decision by subject	3 (1)	4 (2)	7 (3)	3 (1)	4 (2)	9 (4)

a. Subjects may have only one primary reason for discontinuation.
b. 1 subject was enrolled with a history of retinal vein occlusion (RVO) or central serious retinopathy (CSR).
c. 1 subject had a complete response and investigator decided to stop treatment; 1subject had overall deterioration related to pneumonia and non-malignant pleural effusion.
d. 1 subject was not compliant.
e. 1 subject was not compliant; 1 subject was enrolled with a history of RVO or CSR.
f. Treatment was discontinued for 1 subject for better management of visual changes; 1 subject was not compliant; 1 subject had maintained complete response and co-morbidities, therefore it was felt to be in her best interest to stop study treatment.

Figure 7: CONSORT patient flow diagram for COMBI-d (12 January 2015 cut-off) [18]



*Some patients were ineligible for more than one reason.

Patient disposition in COMBI-v

A total of 704 patients were randomised 1:1 to study treatment (trametinib + dabrafenib, N=352; vemurafenib monotherapy N=352). At the time of the latest data cut-off (13 March

2015), 29% of patients in the combination arm and 9% in the vemurafenib monotherapy arm remained on study treatment (Table 20), and 50% and 34% of patients, respectively, were still ongoing in the study (Table 19). This information is also presented as a CONSORT flow diagram in Figure 8.[19; 113]

Crossover was prohibited until the IDMC recommended stopping the study early for efficacy. After the recommendation, patients randomised to the vemurafenib group were allowed to cross over to receive combination therapy; 21 (6%) patients had switched to the combination as of the March 2015 cut-off (only 5 of whom had experienced disease progression).

Table 19: Summary of subject disposition in COMBI-v (ITT population)

	17 April 2014 cut-off[19; 113]		13 March 2015 cut-off[20; 153]	
	Trametinib + dabrafenib N=352	**Vemurafenib monotherapy N=352**	**Trametinib + dabrafenib N=352**	**Vemurafenib monotherapy N=352**
Subject status, n (%)				
Died	100 (28)	122 (35)	155 (44)	194 (55)
Ongoing	236 (67)	202 (57)	176 (50)	119 (34)
Withdrawn from study[a]	16 (5)	28 (8)	21 (6)	36 (10)
Primary reason for early withdrawal, n (%)				
Lost to follow-up	4 (1)	9 (3)	5 (1)	16 (5)
Investigator decision	2 (<1)[a]	1 (<1)[b]	4 (1)	3 (1)
Withdrew consent	10 (3)	18 (5)	12 (3)	20 (6)

a. 1 subject had an eligibility deviation (no histologically confirmed cutaneous melanoma that was either Stage IIIC or Stage IV, and determined to be BRAF V600E/K mutation-positive); 1 subject discontinued study due to being lost to follow up, returned to home country.

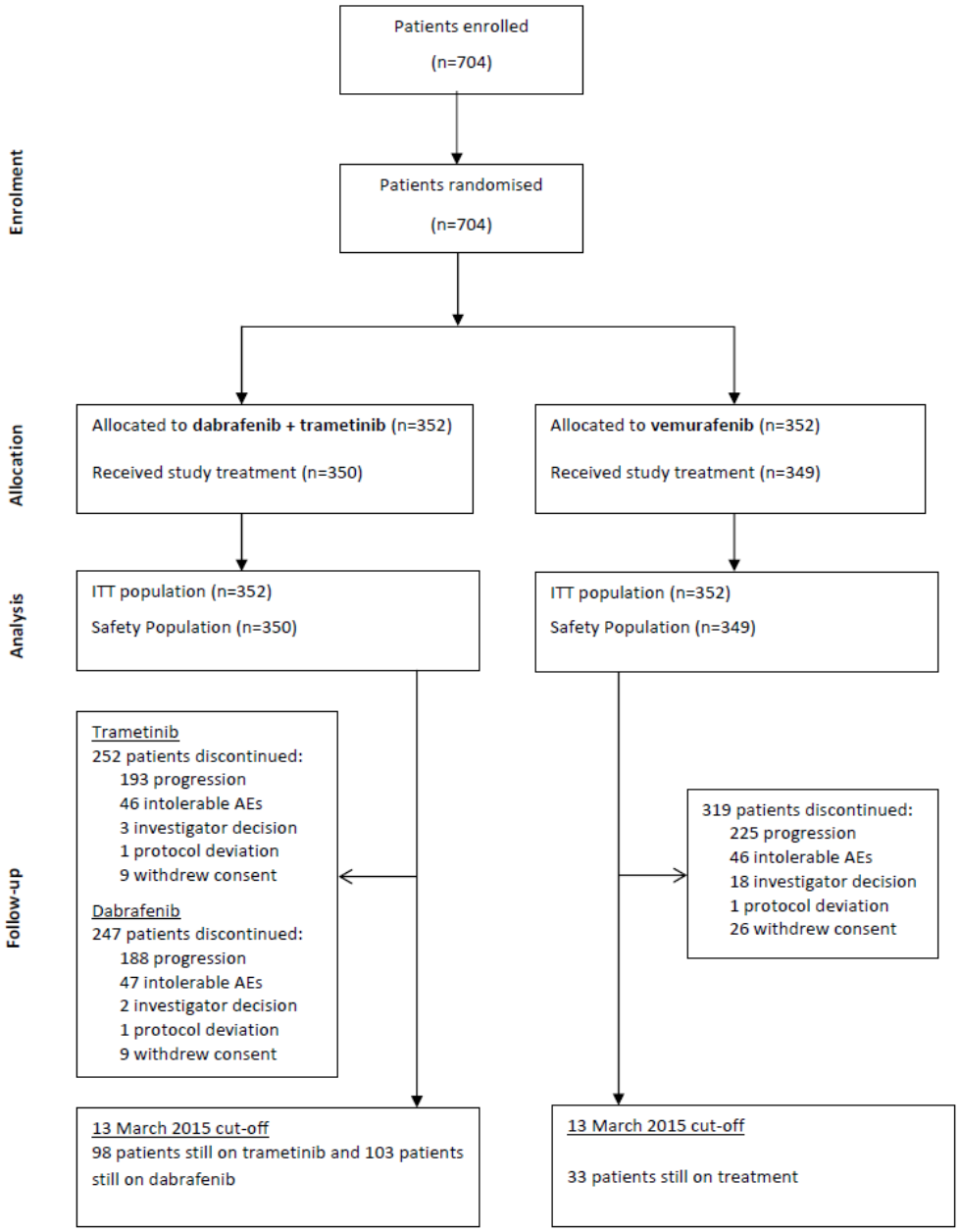
b. 1 subject was not compliant.

Table 20: Treatment status in COMBI-v (ITT population)

	17 April 2014 cut-off[19; 113]			13 March 2015 cut-off[20; 153]		
	Trametinib + dabrafenib N=352		**Vemurafenib mono therapy N=352**	**Trametinib + dabrafenib N=352**		**Vemurafenib mono therapy N=352**
	Dabrafenib	**Trametinib**		**Dabrafenib**	**Trametinib**	
Subject status, n (%)						
Ongoing	169 (48)	169 (48)	89 (26)	103 (29)	98 (28)	33 (9)
Discontinued	181 (52)	181 (52)	260 (74)	247 (71)	252 (72)	316 (91)
Primary reason for discontinuation[a], n (%)						
Disease progression	135 (39)	139 (40)	200 (57)	188 (54)	193 (55)	225 (64)
Adverse event[b]	38 (11)	35 (10)	37 (11)	47 (13)	46 (13)	46 (13)
Investigator decision	1 (<1)	1 (<1)	10 (3)	2 (<1)	3 (<1)	18 (5)
Protocol deviation	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Decision by subject	6 (2)	5 (1)	12 (3)	9 (3)	9 (3)	26 (7)

a. Subjects may have only one primary reason for discontinuation.
b. Because different CRF pages are used to record discontinuation events (AE CRF and Treatment Discontinuation CRF), there some discrepancies between subjects discontinuing study treatment due to an AE in this table and those represented in Table 58 (AEs Leading to Permanent Discontinuation of Study Treatment).

Figure 8: CONSORT patient flow diagram for COMBI-v (13 March 2015 cut-off)[153]



Patient disposition in BRF113220 (Part C)

A total of 162 patients with BRAF mutation-positive stage IIIc or stage IV melanoma were enrolled in BRF113220, Part C; 54 patients were randomised to each treatment arm.[25] Patient disposition at the cut-off date (31 May 2012) for the primary PFS analysis and at the cut-off date for the latest OS analysis (15 January) is summarised in Table 21.

Table 21: Summary of subject disposition in BRF113220 (Part C) (ITT population)

	31 May 2012[25; 114]			15 January 2015[154]		
	Trametinib + dabrafenib 150/2 N=54	Trametinib + dabrafenib 150/1 N=54	Dabrafenib mono-therapy N=54*	Trametinib + dabrafenib 150/2 N=54	Trametinib + dabrafenib 150/1 N=54	Dabrafenib mono-therapy N=54*
Subject status, n (%)						
Died	14 (26)	18 (33)	19 (35)	36 (67)	34 (63)	41 (76)
Ongoing in study	40 (74)	32 (59)	35 (65)*	17 (31)	11 (20)	9 (17)
On study treatment	23 (43)	23 (43)	16 (30)*	6 (11)	6 (11)	3 (6)
In follow-up	17 (31)	9 (17)	19 (35)*	11 (20)	5 (9)	6 (11)
Withdrawn from study	0	4 (7)	0	1 (2)	9 (17)	4 (7)
Primary Reason for early withdrawal[a], n (%)						
Withdrew consent	0	4 (7)	0	0	6 (11)	2 (4)
Investigator discretion	0	0	0	0	1 (2)	0
Lost to follow-up	0	0	0	1 (2)	2 (4)	2 (4)

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

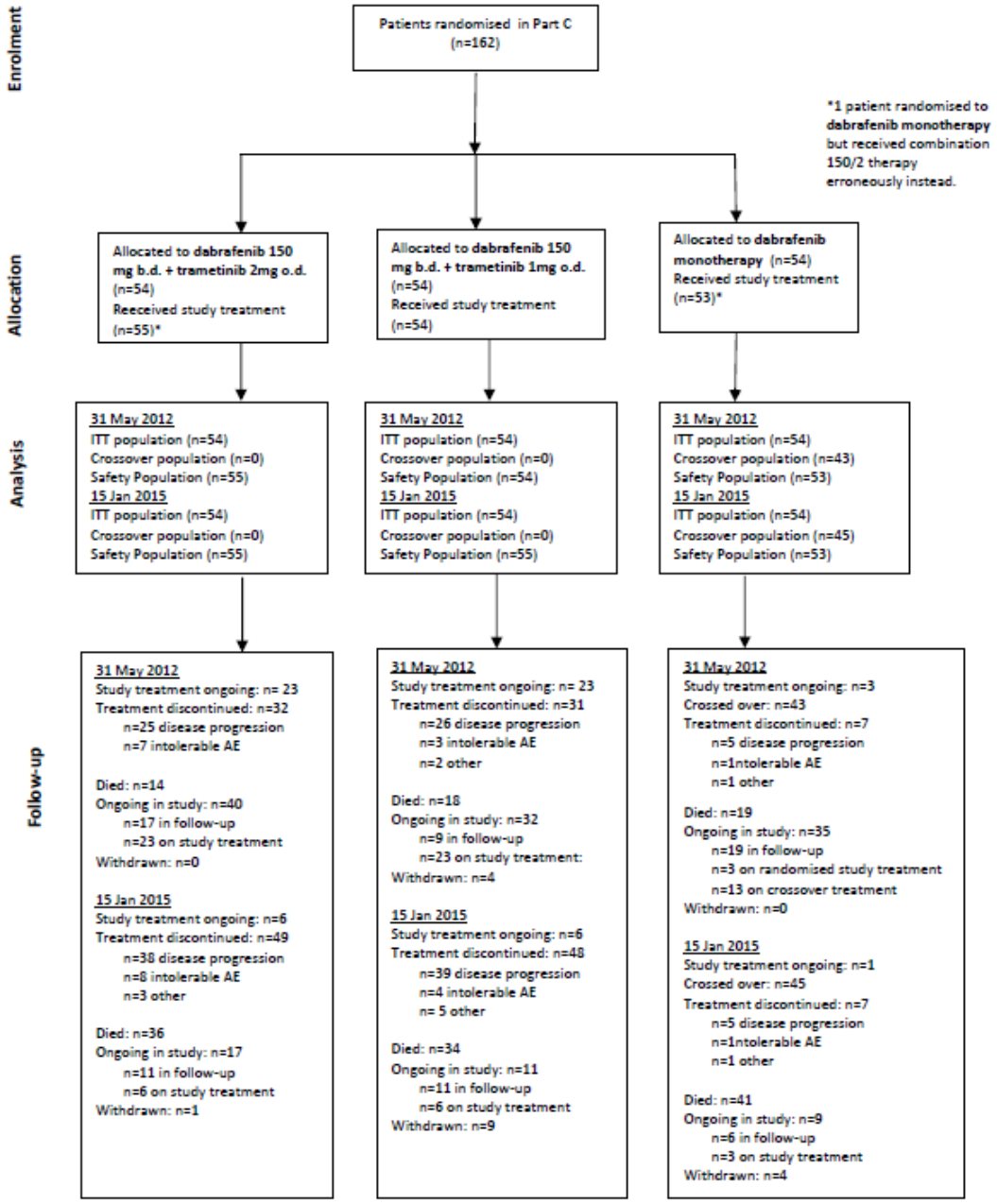
Table 22 summarises study treatment status at the 31 May 2012 and 15 January 2015 cut-offs. (Note that one subject originally randomised to the dabrafenib monotherapy group inadvertently received the combination therapy 150/2 and is therefore included in this group). At the 15 January 2015 cut-off, 45 patients (83%) randomised to the dabrafenib monotherapy group had crossed over to receive combination 150/2 following confirmed disease progression.

Table 22: Summary of treatment status in BRF113220 Part C (All treated population)

	31 May 2012[114]			15 January 2015[154]		
	Trametinib + dabrafenib 150/2 N=55[a]	Trametinib + dabrafenib 150/1 N=54	Dabrafenib mono-therapy N=53[a]	Trametinib + dabrafenib 150/2 N=55[a]	Trametinib + dabrafenib 150/1 N=54	Dabrafenib mono-therapy N=53a
Treatment status, n (%)						
Ongoing	23 (42)	23 (43)	3 (6)	6 (11)	6 (11)	1 (2)
Crossed-over	NA	NA	43 (81)	NA	NA	45 (85)
Discontinued	32 (58)	31 (57)	7 (13)	49 (89)	48 (89)	7 (13)
Primary[b]/Subreason for Treatment Discontinuation, n (%)						
Disease progression	24 (45)	26 (48)	5 (9)	38 (69)	39 (72)	5 (9)
AE	7 (13)	3 (6)	1 (2)	8 (15)	4 (5)	1 (2)
Other	0	2 (4)	1 (2)	3 (6)	5 (10)	1 (2)

a. One subject was randomised to receive dabrafenib monotherapy but instead received combination therapy (150/2), and is therefore included in the combination therapy (150/2) group (having received this treatment) rather than in the monotherapy group.
b. Subjects may have only one primary reason for discontinuation.
NA = Not applicable.

Figure 9: CONSORT patient flow diagram for BRF113220 (Part C)[25; 154]



4.5.2. In a table describe the characteristics of the participants at baseline for each of the trials. Provide details of baseline demographics, including age, gender and relevant variables describing disease severity and duration and if appropriate previous treatments and concomitant treatment. Highlight any differences between trial groups. A suggested table format is presented below.

Baseline demographics and disease characteristics in COMBI-d

Demographic, disease characteristics and prognostic factors were well balanced between the two treatment arms at baseline, with the exception of visceral disease, which was higher

in the combination arm (Table 23).[17; 18] Prior therapies were also consistent between the treatment arms (it should be noted that all prior systemic therapy was in the neoadjuvant or adjuvant setting).[111]

Table 23: Baseline demographics and disease characteristics in the COMBI-d study (ITT population) [17; 18; 110]

	Treatment arms		Total N=423
	Trametinib + dabrafenib N =211	Dabrafenib monotherapy N = 212	
Age, years			
Mean (SD)	55.1 (13.33)	55.3 (13.75)	55.2 (13.52)
Median (min-max)	55.0 (22, 89)	56.5 (22, 86)	56.0 (22, 89)
Sex, n (%)			
Female	100 (47)	98 (46)	198 (47)
Male	111 (53)	114 (54)	225 (53)
Measurable disease at baseline, n (%)			
No	0	1 (<1)	1 (<1)
Yes	210 (>99)	210 (>99)	420 (>99)
Prior Immunotherapy (adjuvant setting), n (%)			
No	154 (73)	151 (71)	305 (72)
Yes	57 (27)	61 (29)	118 (28)
ECOG PS at baseline, n (%)			
ECOG 0	150 (71)	150 (71)	305 (72)
ECOG 1	61 (29)	61 (29)	116 (27)
BRAF mutation status, n (%)[a]			
V600E	179 (85)	181 (85)	360 (85)
V600K[b]	32 (15)	30 (14)	62 (15)
Stage at screening, n (%)			
IVM1c[a]	142 (67)	138 (65)	280 (66)
IIIc, IVM1a, or IVM1b	69 (33)	73 (34)	142 (34)
M stage at screening, n (%)			
M0[a]	5 (2)	10 (5)	15 (4)
M1a	19 (9)	31 (15)	50 (12)
M1b	45 (21)	32 (15)	77 (18)
M1c	142 (67)	138 (65)	280 (66)
Baseline LDH, n (%)			
≤ULN	133 (63)	140 (66)	273 (65)
>ULN	77 (36)	71 (33)	148 (35)
Visceral disease at baseline, n (%)[c]			
No	46 (22)	66 (31)	112 (26)
Yes	165 (78)	145 (68)	310 (73)
Number of disease sites at baseline, n (%)[d]			
≥3 sites	101 (48)	92 (43)	193 (46)
<3 sites	109 (52)	119 (56)	228 (54)
Prior anti-cancer therapy, n (%)[e]			
Any	199 (94)	205 (97)	404 (96)
Chemotherapy	8 (4)	13 (6)	21 (5)
Immunotherapy	56 (27)	61 (29)	117 (28)
Hormonal therapy	0	1 (<1)	1 (<1)
Biologic therapy	2 (<1)	2 (<1)	4 (<1)
Surgery	196 (93)	203 (96)	399 (94)
Radiotherapy	29 (14)	43 (20)	72 (17)

Note: In the trametinib + dabrafenib combination group, one patient was randomised in error, and no baseline data were recorded for this patient in 4 categories (previous immunotherapy, ECOG performance score, lactate dehyrdrogenase, and number of disease sites). In the dabrafenib monotherapy group, one patient was randomised in error, and no baseline data were recorded for this patient.

a. Data are from eCRF, while stratification factors were based upon randomised strata from the Registration and Medication Ordering System.

b. One patient was both BRAF V600E and BRAF V600K mutation positive and is included in the BRAF V600K subset in this display.

c. Defined as the soft internal organs including the lungs, heart, and organs of the digestive, excretory, reproductive, and circulatory systems but excluding lymph nodes.

d. Number of body sites of disease based on unique RECIST target and non-target lesions identified by the investigator, not the number of metastases.

e. Patients may have received more than 1 type of anti-cancer therapy.

b.d. = twice daily; ECOG = Eastern Cooperative Oncology Group; LDH = Lactate dehydrogenase; o.d. = Once daily; SD = Standard deviation; ULN = Upper limit of normal

Baseline demographics and disease characteristics in COMBI-v

Demographic, disease characteristics and prognostic factors were well balanced between the treatment arms at baseline, with the exception of gender and number of disease sites at baseline (Table 24). The combination arm enrolled more males and more patients with ≥3 disease sites than the vemurafenib arm.[19] Prior therapies were generally consistent between the treatment arms, with the exception of prior immunotherapy where more patients had received immunotherapy in the vemurafenib arm (again, all systemic therapy was in the neoadjuvant or adjuvant setting).[113]

Table 24: Baseline demographics and disease characteristics in the COMBI-v study (ITT population) [19; 113]

	Treatment arms		Total
	Trametinib + dabrafenib	Vemurafenib monotherapy	
	N=352	N=352	N=704
Age, years			
Mean (SD)	54.1 (13.83)	54.3 (14.06)	54.2 (13.94)
Median (min-max)	55.0 (18, 91)	54.0 (18, 88)	54.5 (18, 91)
Sex, n (%)			
Female	144 (41)	172 (49)	316 (45)
Male	208 (59)	180 (51)	388 (55)
Measurable disease at baseline, n (%)			
No	0	2 (<1)	2 (<1)
Yes	351 (>99)	350 (>99)	701 (>99)
Prior Immunotherapy (adjuvant setting), n (%)[b]			
No	61 (17)	93 (26)	154 (22)
Yes	61 (17)	93 (26)	154 (22)
ECOG PS at baseline, n (%)			
ECOG 0	248 (71)	248 (70)	496 (70)
ECOG 1	102 (29)	104 (30)	206 (29)
BRAF mutation status, n (%)[d]			
V600E	312 (90)	317 (90)	629 (89)
V600K[c]	34 (10)	34 (10)	68 (10)
V600E & V600K	5 (1)	1 (<1)	6 (<1)
Stage at screening, n (%)			
Stage IIIc, IVM1a, or IVM1b	130 (37)	143 (41)	273 (39)
IIIc[a]	221 (63)	208 (59)	429 (61)
M stage at screening, n (%)			
M0	14 (4)	26 (7)	40 (6)
M1a	55 (16)	50 (14)	105 (15)
M1b	61 (17)	67 (19)	128 (18)
M1c	221 (63)	208 (59)	429 (61)
Unknown	0	1 (<1)	1 (<1)

Baseline LDH, n (%)			
≤ULN	233 (66)	238 (68)	471 (67)
>ULN	118 (34)	114 (32)	232 (33)
Visceral disease at baseline, n (%)[e]			
No	73 (21)	81 (23)	154 (22)
Yes	278 (79)	271 (77)	549 (78)
Number of disease sites at baseline, n (%)[f]			
≥3 sites	174 (50)	151 (43)	325 (46)
<3 sites	177 (50)	201 (57)	378 (54)
Prior anti-cancer therapy, n (%)[g]			
Any	309 (88)	318 (90)	627 (89)
Chemotherapy	13 (4)	6 (2)	19 (3)
Immunotherapy	61 (17)	93 (26)	154 (22)
Biologic therapy	1 (<1)	5 (1)	6 (<1)
Surgery	302 (86)	310 (88)	612 (87)
Radiotherapy	53 (15)	61 (17)	114 (16)

Data are missing in several categories for one patient in each treatment arm because data were either missing or incorrect at baseline. There were no significant differences between the groups at baseline except for gender (p=0.03).

a. Data are from eCRF, while stratification factors were based upon randomised strata from the Registration and Medication Ordering System. Baseline LDH and BRAF mutation status collected in CRF were summarised.

b. Previous immunotherapy included interferon-alfa, interferon-gamma, interleukin-2, granulocyte–macrophage colony-stimulating factor, gangliosides, imiquimod, ipilimumab, and investigational antineoplastic vaccine. Interferon and interleukin were classified as biologics in the clinical database. They were reclassified as immunotherapy in this ad hoc analysis.

c. The one patient (Patient 10642) with wildtype BRAF was not included in this summary and was excluded from all subgroup analyses for BRAF mutation status.

d. Six patients in the combination therapy group and one patient in the vemurafenib monotherapy group had both BRAF V600E and V600K mutations and thus were excluded from either subgroup.

e. Visceral disease was defined as that affecting the soft internal organs, including the lungs, heart and the organs of the digestive, excretory, reproductive and circulatory systems but excluding lymph nodes.

f. The number of disease sites is the number of unique target and non-target lesions, as defined by RECIST and identified by the investigator, not the number of metastases.

g. Patients may have received more than 1 type of anti-cancer therapy.

b.d. = twice daily; ECOG = Eastern Cooperative Oncology Group; LDH = Lactate dehydrogenase; o.d. = Once daily; SD = Standard deviation; ULN = Upper limit of normal

Baseline demographics and characteristics in BRF113220 (Part C).

Baseline demographic, disease characteristics and prognostic factors were broadly similar across the three treatment groups, with the exception that more female subjects were enrolled in the combination arms than the dabrafenib monotherapy arm (Table 25). Prior anti-cancer therapy was also similar across treatment groups; the majority of subjects (81%) in the study had not received prior systemic anti-cancer regimens for advanced or metastatic disease.[25; 114]

Table 25: Baseline demographics and disease characteristics in BRF113220 (Part C) (ITT population) [25; 114]

	Treatment arms			**Total (all dose arms)**
	Dabrafenib 150 mg b.d.	**Dabrafenib 150 mg b.d. + Trametinib 1 mg o.d.**	**Dabrafenib 150 mg b.d. + Trametinib 2 mg o.d.**	
	N=54	**N=54**	**N=54**	**N=162**
Age, years				
Mean (SD)	51.8 (15.19)	49.9 (14.70)	55.9 (11.85)	52.5 (14.13)
Median (min-max)	49.5 (18 – 82)	49.0 (23 – 85)	57.5 (27 – 79)	53.0 (18 – 85)
Sex, n (%)				
Female	25 (46)	24 (44)	20 (37)	69 (43)
Male	29 (54)	30 (56)	34 (63)	93 (57)

ECOG PS at baseline, n (%)				
ECOG 0	34 (63)	38 (70)	35 (65)	107 (66)
ECOG 1	20 (37)	16 (30)	19 (35)	55 (34)
BRAF mutation status, n (%)				
V600E	45 (83)	45 (83)	47 (87)	137 (85)
V600K	9 (17)	9 (17)	7 (13)	25 (15)
Primary tumor type at initial diagnosis, n (%)				
Melanoma	53 (98)	53 (98)	54 (100)	160 (99)
Unknown	1 (2)	1 (2)	0	2 (1)
Stage at screening, n (%)				
IIIc[a]	1 (2)	1 (2)	0	2 (1)
IV	53 (98)	53 (98)	54 (100)	160 (99)
M stage at screening, n (%)				
M0[a]	1 (2)	1 (2)	0	2 (1)
M1a	11 (20)	9 (17)	6 (11)	26 (16)
M1b	5 (9)	11 (20)	10 (19)	26 (16)
M1c	37 (69)	33 (61)	38 (70)	108 (67)
Baseline LDH, n (%)				
≤ULN	27 (50)	29 (54)	32 (59)	88 (54)
>ULN	27 (50)	25 (46)	22 (41)	74 (46)
Prior history of brain metastases, n (%)				
No	50 (93)	47 (87)	52 (96)	149 (92)
Yes	4 (7)	7 (13)	2 (4)	13 (8)
Number of disease sites at baseline, n (%)				
≥3 sites	34 (63)	27 (50)	28 (52)	89 (55)
<3 sites	20 (37)	27 (50)	26 (48)	73 (45)
Prior anti-cancer therapy, n (%)				
Any	53 (98)	50 (93)	53 (98)	156 (96)
Surgery	53 (98)	50 (93)	53 (98)	156 (96)
Radiotherapy	14 (26)	13 (24)	20 (37)	47 (29)
Immunotherapy	8 (15)	16 (30)	13 (24)	37 (23)
Chemotherapy	12 (22)	15 (28)	7 (13)	34 (21)
Biologic therapy	11 (20)	9 (17)	12 (22)	32 (20)
Small molecule targeted therapy	0	1 (2)	1 (2)	2 (1)
Unknown	1 (2)	0	0	1 (<1)
No. of prior advanced/metastatic regimens (chemotherapy or IL-2)				
0	47 (87)	42 (78)	42 (78)	131 (81)
1	4 (7)	10 (19)	11 (20)	25 (15)
2*	3 (6)	1 (2)	0	4 (2)
3*	0	1 (2)	0	1 (<1)
4*	0	0	1 (2)	1 (<1)

a. 2 subjects were classified as Stage IIIcM0

* 6 subjects received prior anti-cancer regimens that could not be easily classified as advanced or metastatic regimens.

b.d. = twice daily; ECOG = Eastern Cooperative Oncology Group; LDH = Lactate dehydrogenase; o.d. = Once daily; SD = Standard deviation; ULN = Upper limit of normal

4.6. Quality assessment of the relevant randomised controlled trials

4.6.1. The validity of the results of an individual RCT will depend on the robustness of its overall design and execution, and its relevance to the decision problem. The quality of each RCT identified in section 4.2 should be appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The quality assessment will be validated by the Evidence Review Group.

The quality assessment for the 3 RCTs relevant to the decision problem: COMBI-d (MEK115306), COMBI-v (MEK116513) and BRF113220 (Part C), are provided in response to question 4.6.3 (Table 26).

4.6.2. Describe the methods used for assessing risk of bias and generalisability of individual RCTs (including whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Responses to the questions for assessment of risk and bias in the RCTs (COMBI-d, COMBI-v, BRF113220 [Part C]) are provided in section 4.6.3 in Table 26.

The management of patients enrolled in the COMBI-d, COMBI-v and BRF113220 (Part C) studies is considered to be reflective of clinical practice in England. The type and timing of assessments undertaken in the RCTs are unlikely to differ significantly from routine clinical practice. Please see response to question 4.13.2 regarding the external validity of the RCTs for further discussion on this subject.

4.6.3. If there is more than 1 RCT, tabulate a summary of the responses applied to each of the quality assessment criteria. A suggested table format for the quality assessment results is presented below.

Responses to the questions for assessment of risk and bias in the RCTs are tabulated below.

Table 26: Critical appraisal of COMBI-d, COMBI-v and BRF113220 (Part C)

Critical appraisal criterion	COMBI-d MEK115306[17; 110]	COMBI-v MEK116513[19; 113]	BRF113220 Part C [25; 114]
Was randomisation carried out appropriately?	Yes. Patients were centrally randomised through the GSK RAMOS (Registration and Medication Ordering System) interactive voice response system (IVRS) in a 1:1 ratio to receive either trametinib + dabrafenib combination therapy or dabrafenib monotherapy. The randomised schedule was computer generated by GSK Biostatistical Department.	Yes. Patients were centrally randomised through the GSK RAMOS (Registration and Medication Ordering System) interactive voice response system (IVRS) in a 1:1 ratio to receive either trametinib + dabrafenib combination therapy or vemurafenib monotherapy. The randomised schedule was computer generated by GSK Biostatistical Department.	Yes. After subjects were approved to enrol in Part C, they were assigned to study treatment (open-label) in accordance with the randomisation schedule generated by Discovery Biometrics, using the GSK RAMOS (Registration and Medication Ordering System) interactive voice recognition system (IVRS)).
Was the concealment of treatment allocation adequate?	Yes. Adequate blinding was achieved by administering placebo tablets (matching trametinib tablets) to	Treatment allocation was not concealed as this was an open-label study.	Treatment allocation was not concealed as this was an open label study.

	subjects randomised to the dabrafenib monotherapy arm. GSK or site staff, or subjects were not aware of the treatment assignment. Every effort was made to maintain the blinding until the final OS analysis was performed. Additionally, a central review of all radiological imaging data was conducted by an independent review committee (IRC) who were blinded to subjects' treatment assignment.		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. Treatment groups were well balanced at baseline in terms of demographic and disease characteristics (gender, ECOG performance status, BRAF mutation status, disease stage, baseline LDH, number of metastatic sites).	Yes. Treatment groups were generally well balanced at baseline in terms of most demographic and disease characteristics (except gender and number of disease sites; there were slightly more males and more patients with <3 disease sites in the vemurafenib arm than the combination arm).	Yes. Treatment groups were well balanced at baseline in terms of demographic and disease characteristics (gender, ECOG performance status, BRAF mutation status, disease stage, baseline LDH, number of metastatic sites, prior therapy).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. Treatment assignment remained blinded to GSK staff, study investigators and site staff and patients throughout the study treatment period. Only in the case of an emergency when knowledge of the study treatment was essential for the clinical management or welfare of the subject could the investigator unblind a subject's treatment assignment.	COMBI-v was an open-label study and treatment was not blinded.	BRF113220 was an open-label study and treatment was not blinded, although a Blinded Independent Central Review (BICR) was introduced following a protocol amendment to support Part C as a potential registration trial. This was used in sensitivity analysis of PFS to address and evaluate potential sources of bias and demonstrate robustness of the effect on PFS.
Were there any unexpected imbalances in drop-outs between groups?	No. Withdrawals were balanced between treatment groups and reasons for patient withdrawals were reported adequately. Patients primarily withdrew from the study due to withdrawal of consent (see Table 17 and Table 18).	No. Reasons for withdrawal of patients were reported adequately; slightly more patients withdrew due to withdrawal of consent in the vemurafenib arm (Table 19 and Table 20).	No. Reasons for withdrawal of patients were reported adequately. Patients who withdrew did so due to withdrawal (Table 21 and Table 22).

Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. The authors reported the outcomes as specified in the protocol of the study.	No. The authors reported all the outcomes as specified in the protocol of the study.	No. The authors reported all the outcomes as specified in the protocol of the study.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. An ITT analysis was used for the analysis of efficacy endpoints and appropriate methods were used to account for missing data.	Yes. An ITT analysis was used for the analysis of efficacy endpoints and appropriate methods were used to account for missing data.	Yes. An ITT analysis was used for the analysis of efficacy endpoints and appropriate methods were used to account for missing data.
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)			

4.7. Clinical effectiveness results of the relevant randomised controlled trials

A summary of the key efficacy results from all three RCTs based on the latest data cuts is provided in Table 70 (section 4.13.1). Full details in relation to these endpoints are provided in sections 4.7.1 (COMB-d), 4.7.2 (COMBI-v) and 4.7.3 (BRF113220 [Part C]) below. For BRF113220, results are only presented for the trametinib + dabrafenib combination 150/2 arm and the dabrafenib monotherapy arm (i.e. not for the combination 150/1 arm since this is not relevant to the decision problem). Results for the crossover population in BRF113220 can be found in Appendix 8.8. Results of OS adjustments for treatment crossover are also provided for COMBI-v and BRF113220 (Part C) in section 4.7.4 (Table 48).

4.7.1 COMBI-d (MEK115306) Results

4.7.1.1 COMBI-d Primary endpoint

Progression-free survival

At the time of initial August 2013 cut-off, there was a 25% reduction in the risk of progression or death for trametinib + dabrafenib combination therapy versus dabrafenib monotherapy. Median PFS was 9.3 months in the combination arm and 8.8 months in monotherapy arm (Table 27), which is longer than previously observed with dabrafenib monotherapy.[14; 25] An assessment by a blinded independent review committee (BIRC) was carried out as a pre-specified analysis; the result was consistent with that observed by investigator assessment (median PFS was 10.1 months for the combination arm versus 9.5 months for the monotherapy arm (HR=0.78 [95% CI 0.59-1.04, p=0.085]).[110]

A more mature PFS analysis was conducted at the time of the final OS analysis (January 2015 cut-off) which demonstrated an improved 33% reduction in the risk of progression or death (Table 27). Median PFS for the trametinib + dabrafenib group was longer (11.0 months) than reported in the primary analysis while median PFS for the dabrafenib

monotherapy group was unchanged at 8.8 months.[18] It should be noted that this updated analysis of PFS was not pre-planned and the p-value was not adjusted for multiple testing.

The respective Kaplan-Meier PFS curves are presented in Figure 10 and Figure 11.

Table 27: Investigator-assessed PFS in COMBI-d (ITT population)

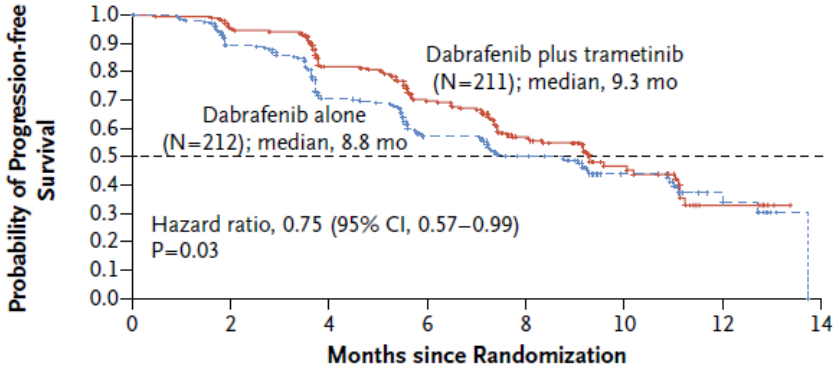
	26 August 2013 cut-off[17]		12 January 2015 cut-off[18]	
	Trametinib + dabrafenib N=211	**Dabrafenib monotherapy N=212**	**Trametinib + dabrafenib N=211**	**Dabrafenib monotherapy N=212**
Patient classification, n (%)				
Progressed or died (event)	102 (48)	109 (51)	139 (66)	162 (76)
Censored, follow-up ended	14 (7)	22 (10)	17 (8)	20 (9)
Censored, follow-up ongoing	95 (45)	81 (38)	55 (26)	30 (14)
Estimates for PFS, months[a]				
1st quartile (95% CI)	5.6 (4.8, 6.5)	3.7 (3.6, 5.3)	5.5 (4.8, 6.2)	3.7 (3.5, 5.0)
Median (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)
3rd quartile (95% CI)	NR (11.2, NR)	13.7 (1.0, 13.7)	NR (24.0, NR)	16.3 (12.9, 18.5)
Adjusted hazard ratio[b]				
Estimate (95% CI)	0.75 (0.57, 0.99)		0.67 (0.53, 0.84)	
Stratified log rank p-value[b]	0.035		0.0004	

a. Quartiles were estimated using the Brookmeyer Crowley method.

b. Hazard ratios are estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with trametinib + dabrafenib compared with monotherapy. Hazard ratio and p-value from stratified log-rank test are adjusted for randomised strata: baseline LDH and BRAF mutation status.

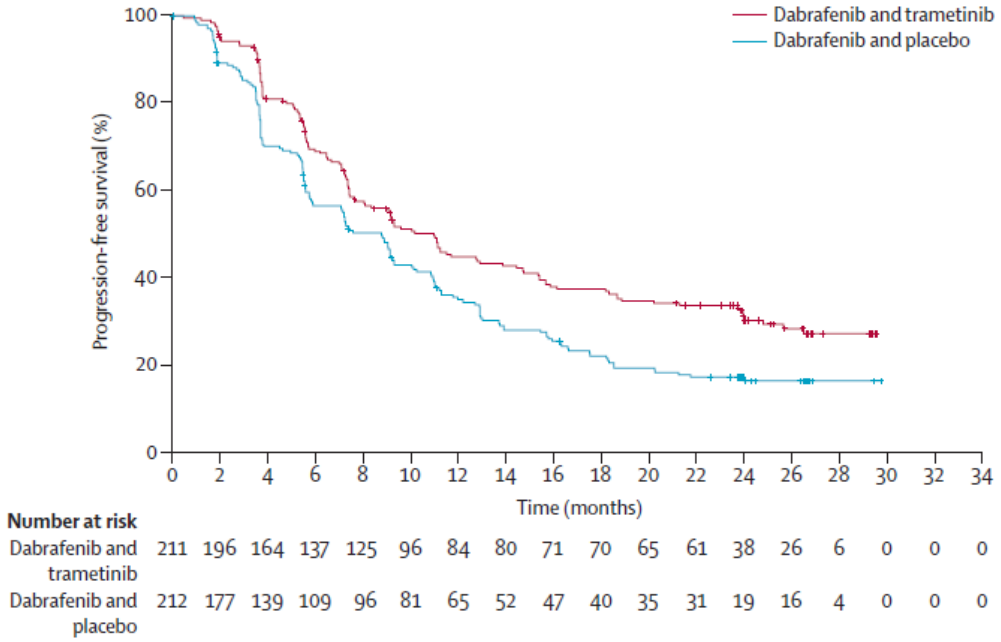
NR = Not reported.

Figure 10: Kaplan-Meier Curves for investigator-assessed PFS in COMBI-d (ITT population, August 2013 cut-off) [17]



No. at Risk								
Dabrafenib plus trametinib	211	196	164	138	82	33	9	0
Dabrafenib alone	212	173	136	107	68	31	10	0

Figure 11: Kaplan-Meier Curves for investigator-assessed PFS in COMBI-d (ITT population, January 2015 cut-off) [18]



Sensitivity analyses of PFS

Sensitivity analyses were performed to demonstrate the robustness of the treatment effect on PFS. Each of the sensitivity analyses on the January 2015 data demonstrated consistency with the HR (0.66-0.67) reported in the primary PFS analysis (Table 28).[111]

Table 28: Sensitivity analyses of investigator-assessed PFS in COMBI-d (ITT population, January 2015 cut-off) [111]

Sensitivity analysis		**Treatment arms**	
		Trametinib + dabrafenib N=211	**Dabrafenib monotherapy N=212**
Including Symptomatic Progression as an event	**Estimates for PFS, months**		
	Median (95% CI)	10.2 (8.0, 12.9)	7.4 (5.8, 9.3)
	Adjusted hazard ratio[a]		
	Estimate (95% CI)	0.66 (0.53, 0.83)	
	Stratified log rank p-value[a]	p<0.001	
Considering start of new anti-cancer therapy or extended loss to follow-up as an event	**Estimates for PFS, months**		
	Median (95% CI)	10.2 (8.1, 12.7)	7.6 (5.8, 9.3)
	Adjusted hazard ratio[a]		
	Estimate (95% CI)	0.66 (0.53, 0.82)	
	Stratified log rank p-value[a]	p<0.001	
Considering progression after start of new anti-cancer therapy or after extended loss to follow-up as an event	**Estimates for PFS, months**		
	Median (95% CI)	9.3 (7.5, 11.7)	7.3 (5.7, 9.1)
	Adjusted hazard ratio[a]		
	Estimate (95% CI)	0.67 (0.53, 0.83)	
	Stratified log rank p-value[a]	p<0.001	

a. Hazard ratios are estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with trametinib + dabrafenib compared with monotherapy. Hazard ratio and p-value from stratified log-rank test are adjusted for randomised strata: baseline LDH and BRAF mutation status.

4.7.1.2 COMBI-d Secondary endpoints

Overall survival

Although the OS data were not mature as of the August 2013 cut-off (median follow-up time of 9 months), an effect favouring the combination therapy arm was observed in the planned interim OS analysis (Table 29).[17]

At the final OS analysis, median OS was 25.1 months for the trametinib + dabrafenib combination arm compared with 18.7 months for the dabrafenib monotherapy arm, representing a 29% reduction in the risk of death (Table 29 and Figure 12).[18] One-year and 2-year survival were both greater in the trametinib + dabrafenib group than the dabrafenib monotherapy group.[18]

Table 29: Overall survival in COMBI-d (ITT population)

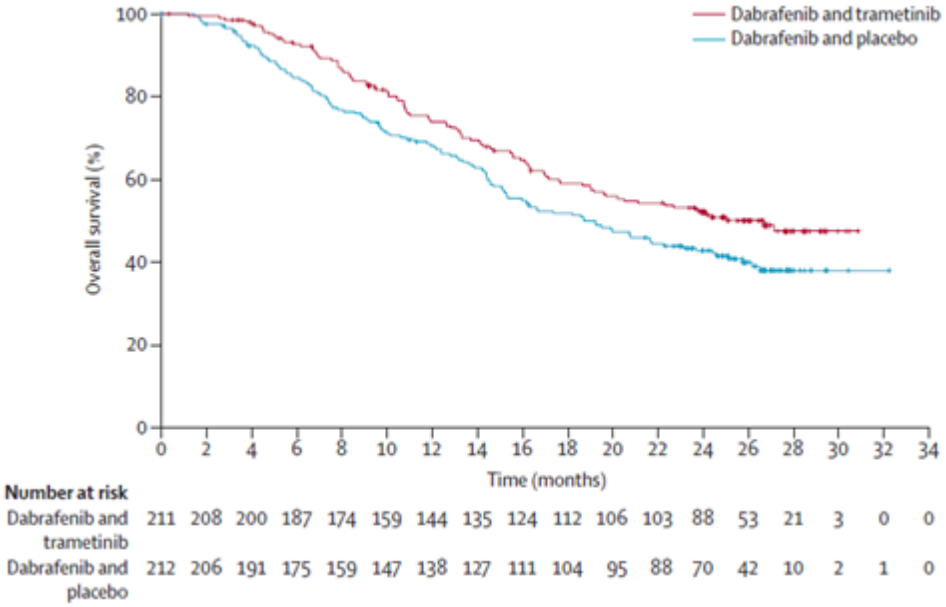
	26 August 2013 cut-off[17]		**12 January 2015 cut-off[18]**	
	Trametinib + dabrafenib N=211	**Dabrafenib monotherapy N=212**	**Trametinib + dabrafenib N=211**	**Dabrafenib monotherapy N=212**
Patient classification, n (%)				
Died (event)	40 (19)	55 (26)	99 (47)	123 (58)
Censored, follow-up ended	17 (8)	10 (5)	19 (9)	13 (6)
Censored, follow-up ongoing	154 (73)	147 (69)	93 (44)	76 (36)
Estimates for PFS, months[a]				
1st quartile (95% CI)	13.7 (10.1, NR)	9.2 (7.1, NR)	8.9 (7.1, 11.8)	8.9 (7.1, 11.8)
Median (95% CI)	NR (14.1, NR)	NR (NR, NR)	18.7 (15.2, 23.7)	18.7 (15.2, 23.7)
3rd quartile (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
Adjusted hazard ratio[b]				
Estimate (95% CI)	0.63 (0.42, 0.94)		0.71 (0.55, 0.92)	
Stratified log rank p-value[b]	p=0.023		0.0107	
Estimates for overall survival at 1 year and 2 years, %				
1 year (95% CI)	NA	NA	74% (67, 79)	68% (61, 74)
2 year (95% CI)	NA	NA	51% (44, 58)	42% (35, 49)

a. Quartiles were estimated using the Brookmeyer Crowley method.

b. Hazard ratios are estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with trametinib + dabrafenib compared with monotherapy. Hazard ratio and p-value from stratified log-rank test are adjusted for randomised strata: baseline LDH and BRAF mutation status.

NA = Not available; NR = Not reached.

Figure 12: Kaplan-Meier Curves for OS in COMBI-d (ITT population, January 2015 cut-off) [18]



The OS benefit was observed despite more patients in the dabrafenib monotherapy group receiving subsequent systemic anti-cancer treatments after progression than in the combination group (51% vs. 33%). A similar number of patients continued their assigned study treatment after progression (Table 30).[18]

Table 30: Subsequent anti-cancer therapy in COMBI-d (ITT population, January 2015 cut-off) [18]

	Treatment arms	
	Dabrafenib + trametinib N=211	**Dabrafenib monotherapy N=212**
Post-progression study treatment, n (%)		
Received assigned study treatment for at least 15 days after disease progression	62 (29)	65 (31)
Follow-up anti-cancer therapy*, n (%)		
Any medication	**70 (33)**	**108 (51)**
Ipilimumab	37 (18)	59 (28)
Dacarbazine	16 (8)	24 (11)
Vemurafenib	16 (8)	23 (11)
Paclitaxel	8 (4)	13 (6)
PD1 inhibitors†	6 (3)	14 (7)
Fotemustine	8 (4)	8 (4)
Carboplatin	8 (4)	7 (3)
Temzolomide	10 (5)	5 (2)
Dabrafenib	5 (2)	8 (4)
Cisplatin	4 (2)	7 (3)
Lomustine	3 (1)	5 (2)
Bevacizumab	1 (<1)	5 (2)

*Assigned study treatment is not included in follow-up therapy.

†Combines pembrolizumab and nivolumab.

Overall response rate (ORR) and duration of response

The confirmed ORR as assessed by investigators was significantly higher in the trametinib + dabrafenib combination arm compared with the dabrafenib monotherapy arm at both the initial and updated cut-offs (Table 31).[17; 18] An ORR based on assessments by the BIRC was calculated at the time of the initial analysis and found to be similar to the investigator-assessed results.[110] At the January 2015 cut-off, more patients had achieved a complete response in the trametinib + dabrafenib group than in the dabrafenib monotherapy group, and the median duration of response was longer (Table 31).[18] Censoring occurred where the response was still ongoing at the time of the analysis in 35% and 26% of patients in the combination arm and dabrafenib monotherapy arm, respectively.[111]

Table 31: Investigator-assessed responses in COMBI-d (ITT population)

	26 August 2013 cut-off[17]		**12 January 2015 cut-off[18]**	
	Trametinib + dabrafenib N=211	**Dabrafenib monotherapy N=212**	**Trametinib + dabrafenib N=211**	**Dabrafenib monotherapy N=212**
Best response[a], n (%)				
CR	22 (10)	18 (9)	33 (16)	28 (13)
PR	118 (56)	90 (43)	111 (53)	84 (40)
SD	54 (26)	69 (33)	50 (24)	66 (31)
PD	13 (6)	19 (9)	13 (6)	19 (9)
NE	3 (1)	14 (7)	3 (1)	13 (6)
ORR, n (%)				
CR + PR	140 (67)	108 (51)	144 (69)	112 (53)
95% CI	(59.9, 73.0)	(44.5, 58.4)	(61.8, 74.8)	(46.3, 60.2)
Difference in ORR				
Difference	15		15%[c]	
95% CI	(5.9, 24.5)		(6.0, 24.5)	
p-value[b]	p=0.0015		p=0.0014	
Duration of response, months				
	n=140	n=108	n=144	n=112
Median	9.2	10.2	12.9	10.6
95% CI	(7.4, NR)	(7.5, NR)	(9.4, 19.5)	(9.1, 13.8)

a. Best response includes only patients who had measurable disease at baseline (210 in each treatment arm).
b. Chi-squared test was used to calculate the p-value.
c. Note that the difference in response rates was calculated prior to rounding the response rates to whole numbers.

4.7.1.3 COMBI-d Health-related quality of life (HRQoL)

The HRQoL data for COMBI-d presented in this submission relate to the 26 August 2013 cut-off for the primary PFS analysis consistent with the HRQoL data used in the economic model. The HRQOL results at the time of the final OS analysis (January 2015 cut-off) were similar to and consistent with the data presented below.

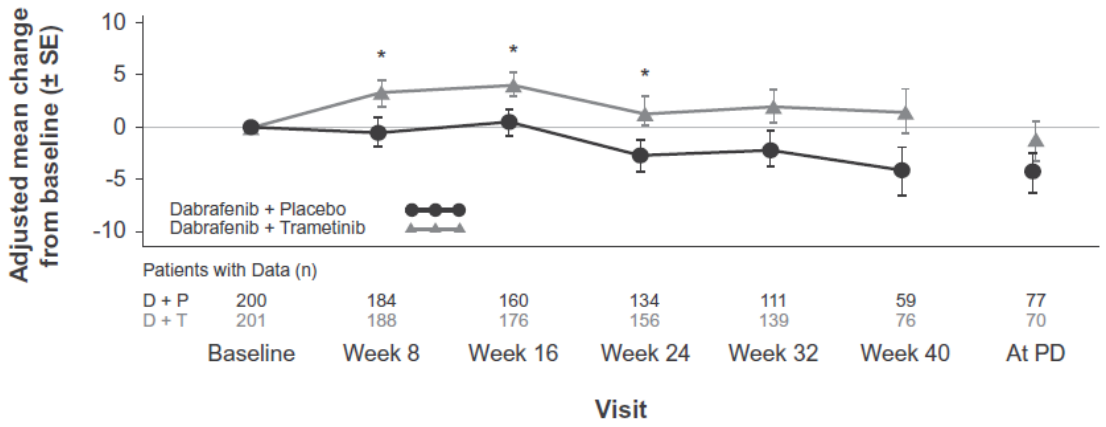
European Organisation for Research and Treatment of Cancer Quality of Life C-30 Questionnaire (EORTC-QLQ-C30)

Completion rates for the EORTC-QLQ-C30 questionnaire as a percentage of available patients were >90% at baseline and at weeks 8, 16, 24, 32 and 40 and >70% at disease progression in both treatment arms. At baseline, patients in both arms reported comparable levels of global health status and functional and symptom-related HRQoL scores, with differences of <5 points in mean scores in all of the dimensions.[28]

Global health status

Overall HRQoL as measured by the global health status score was consistently better (statistically significantly better ($p<0.05$) at weeks 8, 16 and 24; and clinically meaningful at week 40) for patients receiving trametinib + dabrafenib combination therapy compared with those receiving dabrafenib monotherapy during treatment (3.7- to 5.8-point difference) and at disease progression (3-point difference (Figure 13).[28]

Figure 13: Change from baseline in Global Health Status in COMBI-d (ITT population, August 2013) [28]



* Denotes $p<0.05$ at week 8, 16, and 24. Differences were clinically meaningful at week 40.
PD = Progression disease; SE = Standard error.

Functional dimensions

For five functional dimensions (physical, social, role, emotional, and cognitive functioning) of the EORTC-QLQ-C30, the majority of scores trended in favour of trametinib + dabrafenib compared with the dabrafenib monotherapy (Table 32). Of these, role functioning consistently showed the most improvements (4–6 points) over the assessment time points for patients receiving combination therapy.[28]

Table 32: Summary of EORTC QLQ-C30 functional domain scores in COMBI-d (ITT population, August 2013 cut-off) [28]

Functional domain	Differences in change from baseline scores (dabrafenib plus trametinib vs dabrafenib) with 95% CI					
	Week 8	Week 16	Week 24	Week 32	Week 40	PD
Physical functioning	1.86 (–0.89 - 4.60)	4.05 (1.20 - 6.89)[a]	3.01 (–0.22 - 6.24)	3.07 (–0.36 - 6.49)	4.93 (0.70 - 9.17)[a]	3.24 (–0.70 - 7.18)
Role functioning	4.41 (–0.07 - 8.90)	4.58 (–0.11 - 9.27)	5.36[b] (0.01 - 10.71)[a]	5.85[b] (0.15 - 11.55)[a]	5.26[b] (–1.67 - 12.19)	5.40[b] (–0.84 - 11.64)
Emotional functioning	1.87 (–1.66 - 5.40)	1.78 (–1.63 - 5.19)	0.99 (–2.61 - 4.59)	0.12 (–4.17 - 4.42)	4.23 (–1.34 - 9.79)	2.27 (–2.50 - 7.04)
Cognitive functioning	1.08 (–1.82 - 3.98)	–0.55 (–3.52 - 2.42)	–1.24 (–4.59 - 2.11)	–0.08 (–3.56 - 3.40)	5.68[b] (1.12 - 10.23)[a]	–0.29 (–4.26 - 3.68)
Social functioning	2.99 (–1.25 - 7.23)	2.24 (–1.82 - 6.30)	2.18 (–2.15 - 6.50)	5.38[b] (0.40 - 10.37)[a]	6.20[b] (0.07 - 12.32)[a]	2.33 (–3.01 - 7.68)

Favors dabrafenib + trametinib

Favors dabrafenib monotherapy

Positive values indicate improvement in health status; negative values indicate decline.
a. Statistically significant (P < 0.05). b. Clinically meaningful difference.

Symptom dimensions

In terms of the symptom-related dimensions of the EORTC-QLQ-C30, pain scores were statistically significantly (p<0.05) and clinically meaningfully better for patients receiving trametinib + dabrafenib compared with those receiving dabrafenib monotherapy at all follow-up assessments. Fatigue and insomnia trended in favour of trametinib + dabrafenib over dabrafenib monotherapy. For the other symptom-related dimensions, scores were either comparable between the treatment arms or trended in favour of dabrafenib monotherapy (Table 33).[28]

Table 33: Summary of EORTC QLQ-C30 symptom domain scores in COMBI-d (ITT population, August 2013 cut-off) [28]

Symptom domain	Differences in change from baseline scores (dabrafenib plus trametinib vs dabrafenib) with 95% CI					
	Week 8	Week 16	Week 24	Week 32	Week 40	PD
Fatigue	0.95 (–3.30 - 5.21)	–2.32 (–6.33 - 1.68)	–2.63 (–6.95 - 1.70)	–3.09 (–8.03 - 1.85)	–4.08 (–10.54 - 2.39)	–3.43 (–8.63 - 1.77)
Nausea and vomiting	1.32 (–1.46 - 4.09)	2.65 (0.28 - 5.03)[a]	3.73 (0.89 - 6.56)[a]	1.48 (–0.94 - 3.89)	1.85 (–1.92 - 5.61)	2.17 (–1.22 - 5.57)
Pain	–6.25[b] (–10.65 - –1.85)[a]	–8.16[b] (–12.67 - –3.65)[a]	–10.28[b] (–15.26 - –5.31)[a]	–7.09[b] (–12.82 - –1.35)[a]	–12.57[b] (–19.39 - –5.75)[a]	–12.09[b] (–18.25 - –5.93)[a]
Dyspnoea	1.08 (–2.57 - 4.73)	1.31 (–2.49 - 5.11)	2.62 (–1.39 - 6.62)	0.42 (–4.00 - 4.83)	–0.36 (–4.52 - 3.81)	0.14 (–4.70 - 4.97)
Insomnia	–0.26 (–5.01 - 4.50)	–2.99 (–7.54 - 1.56)	–3.51 (–8.69 - 1.67)	–2.82 (–8.12 - 2.48)	–6.86[b] (–14.40 - 0.67)	–5.74[b] (–12.08 - 0.61)
Appetite loss	2.06 (–2.40 - 6.52)	0.63 (–3.22 - 4.49)	–0.90 (–5.14 - 3.33)	1.29 (–2.93 - 5.52)	–0.77 (–7.52 - 5.98)	–3.09 (–8.29 - 2.10)
Constipation	3.15 (–0.45 - 6.74)	0.73 (–3.10 - 4.56)	1.42 (–1.79 - 4.63)	0.96 (–3.32 - 5.25)	–2.22 (–7.50 - 3.06)	–1.28 (–5.30 - 2.74)
Diarrhea	1.79 (–1.53 - 5.11)	1.39 (–2.19 - 4.98)	2.81 (–0.52 - 6.13)	2.06 (–1.23 - 5.35)	NR	1.40 (–2.69 - 5.48)
Financial difficulties	–0.84 (–5.30 - 3.62)	–0.98 (–5.19 - 3.23)	–0.17 (–4.58 - 4.24)	1.89 (–3.07 - 6.85)	–5.50[b] (–11.53 - 0.52)	0.71 (–5.15 - 6.56)

Favors dabrafenib + trametinib

Favors dabrafenib monotherapy

Negative values indicate improvement in symptom; positive values indicate worsening.
a. Statistically significant (P < 0.05). b. Clinically meaningful difference. Abbreviations:
NR = Not reported since mixed model did not converge.

EuroQoL-5D questionnaire (EQ-5D)

For the thermometer scale or VAS, scores were comparable between the treatment arms at baseline (71.7 vs 70.3 for trametinib + dabrafenib and dabrafenib monotherapy, respectively). Health utility scores were also comparable between the treatment arms at baseline (0.765 and 0.730 for the combination therapy and dabrafenib monotherapy, respectively).[110]

Thermometer and utility scores

Following an assessment for differences between treatment arms using mixed-model repeated measures analyses, thermometer scores trended in favour of trametinib + dabrafenib combination therapy versus dabrafenib monotherapy for all assessments until progressive disease, with a statistically significant improvement observed at week 40 (5.88 point; p=0.032). For health utility scores, differences between treatment arms also trended in favour of the combination arm versus dabrafenib monotherapy for all assessments including the progressive disease assessment with a statistically significant improvement observed at week 16 (0.05 point; p=0.007) (Table 34).[110]

Table 34: Summary of Thermometer and Utility Scores for EQ-5D in COMBI-d (ITT Population, August 2013 cut-off) [110]

	Change from Baseline to	Dabrafenib + Trametinib (N=211)			Dabrafenib + Placebo (N=212)			Diff. vs Dabrafenib + Placebo	95% CI for Diff	P-value for Diff.
		n	Adjusted Mean	SE	n	Adjusted Mean	SE			
Thermometer score	Week 8	188	2.47	1.383	181	0.20	1.414	2.26	(-1.63, 6.15)	0.254
	Week 16	173	3.63	1.274	158	1.30	1.325	2.33	(-1.28, 5.94)	0.206
	Week 24	156	1.73	1.292	131	1.64	1.368	0.09	(-3.61, 3.79)	0.964
	Week 32	139	1.49	1.403	106	0.65	1.532	0.83	(-3.25, 4.92)	0.689
	Week 40	73	3.26	1.826	54	-2.62	2.042	5.88	(0.51, 11.25)	0.032[a]
	At PD	71	-1.91	1.540	78	-0.20	1.561	-1.71	(-6.01, 2.60)	0.436
Utility score	Week 8	186	0.06	0.013	184	0.03	0.013	0.04	(-0.00, 0.07)	0.051
	Week 16	173	0.07	0.014	161	0.01	0.014	0.05	(0.01, 0.09)	0.007[a]
	Week 24	155	0.05	0.015	134	0.01	0.015	0.04	(-0.00, 0.08)	0.072
	Week 32	141	0.03	0.016	109	0.00	0.018	0.03	(-0.02, 0.07)	0.261
	Week 40	72	0.01	0.024	57	-0.05	0.026	0.06	(-0.01, 0.13)	0.069
	At PD	68	0.04	0.021	77	-0.01	0.021	0.05	(-0.01, 0.11)	0.110

Summary of Mixed-Model Repeated Measures Analysis for Change from Baseline in Thermometer and Utility Scores for EQ-5D. a. p<0.05. PD=Progressive disease.

Summary of HRQoL assessments in COMBI-d

These analyses demonstrate that the combination of trametinib + dabrafenib improves HRQoL versus dabrafenib monotherapy consistent with the PFS and OS benefits that the combination offers to patients. Based on the EORTC-QLQ-C30, global health status was consistently better for patients receiving trametinib + dabrafenib compared with those receiving dabrafenib monotherapy (significant at weeks 8, 16 and 24) and pain scores were significantly and clinically meaningfully improved for patients receiving combination therapy at all assessments.

4.7.2 COMBI-v (MEK116513) Results

4.7.2.1 COMBI-v Primary endpoint

Overall survival

The interim analysis (April 2014 cut-off; median follow-up time 11 months) demonstrated a significant increase in OS in the trametinib + dabrafenib arm compared with the vemurafenib monotherapy arm. Median OS had not been reached in the combination group and was 17.2 months for patients on vemurafenib (Table 35).

In an updated OS analysis (March 2015 cut-off; median follow-up time 19 months), median OS was 25.6 months in the trametinib + dabrafenib arm and 18.0 months in the vemurafenib monotherapy arm, equating to a 34% reduction in the risk of death (Table 35). The Kaplan-Meier OS curves separate early within 3 months and remain separated throughout the follow-up time (Figure 14).

Table 35: Overall survival in COMBI-v (ITT population)

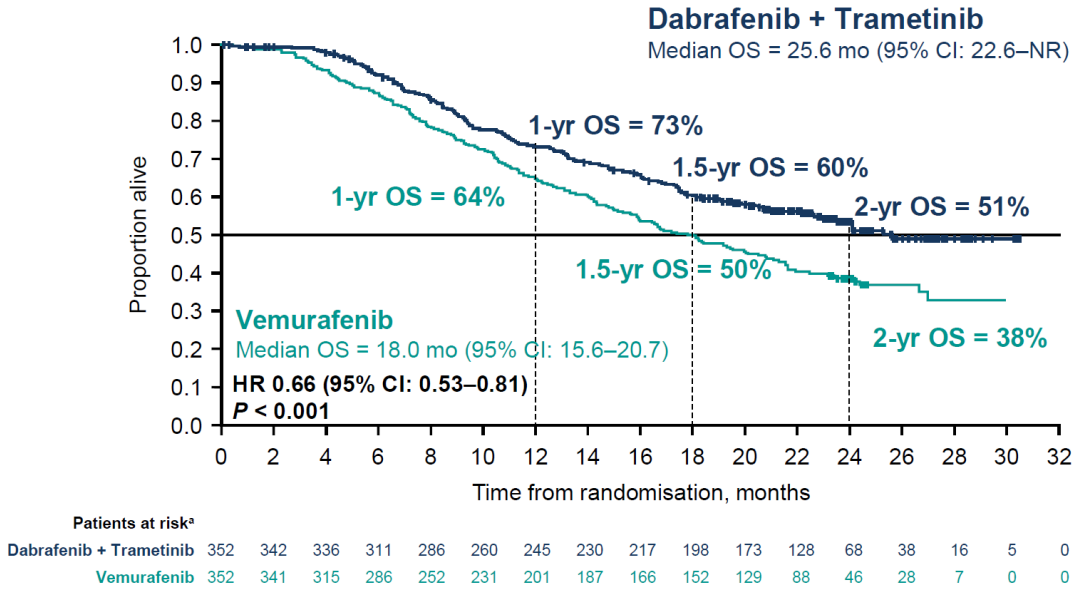
	17 April 2014 cut-off[19]		**13 March 2015 cut-off[20]**	
	Trametinib + dabrafenib N=352	**Vemurafenib monotherapy N=352**	**Trametinib + dabrafenib N=352**	**Vemurafenib monotherapy N=352**
Patient classification, n (%)				
Died (event)	100 (28)	122 (35)	155 (44)	194 (55)
Censored, follow-up ended	16 (5)	28 (8)	21 (6)	39 (11)
Censored, follow-up ongoing	236 (67)	202 (57)	176 (50)	119 (34)
Estimates for PFS, months[a]				
1st quartile (95% CI)	10.9 (9.3, 13.8)	8.9 (7.8, 10.4)	11.1 (9.4, 13.2)	9.1 (7.8, 10.5)
Median (95% CI)	NR (18.3, NR)	17.2 (16.4, NR)	25.6 (22.6, NR)	18.0 (15.6, 20.7)
3rd quartile (95% CI)	NR (NR, NR)	NR (18.0, NR)	NR (NR, NR)	NR (18.0, NR)
Adjusted hazard ratio[b]				
Estimate (95% CI)	0.69 (0.53, 0.89)		0.66 (0.53, 0.81)	
Stratified log rank p-value[b]	p=0.005		p<0.001	
Estimates for overall survival at 1 year and 2 years, %				
1 year (95% CI)	72% (67, 77)	NA	73% (68, 77)	64% (59, 69)
2 year (95% CI)	65% (59, 70)	NA	51% (45, 57)	38% (32, 44)

a. Quartiles were estimated using the Brookmeyer Crowley method.

b. Hazard ratios are estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with trametinib + dabrafenib compared with monotherapy. Hazard ratio and p-value from stratified log-rank test are adjusted for randomised strata: baseline LDH and BRAF mutation status.

NA = Not available; NR = Not reached.

Figure 14: Kaplan-Meier Curves for OS in COMBI-v (ITT population, March 2015 cut-off) [20]



To evaluate a potential influence of subsequent anti-cancer therapies on patients' survival, treatments received in each group after progression were analysed. More patients in the vemurafenib group received subsequent anti-cancer therapies after progression than in the combination group (51% vs. 34%) (Table 36).

Table 36: Summary of follow-up therapy (>2% in any treatment arm) in COMBI-v (ITT population, March 2015 cut-off) [20]

Follow-up anti-cancer therapy, n (%)	Treatment arms	
	Trametinib + dabrafenib N=352	Vemurafenib monotherapy N=352
Any medication	**119 (34)**	**178 (51)**
Ipilimumab	75 (21)	102 (29)
Vemurafenib	31 (9)	34 (10)
Dabrafenib	18 (5)	47 (13)
Dacarbazine	18 (5)	39 (11)
Pembrolizumab	18 (5)	24 (7)
Carboplatin	10 (3)	9 (3)
Paclitaxel	9 (3)	7 (2)
Fotemustine	7 (2)	9 (3)
Nivolumab	7 (2)	4 (1)
Temozolomide	6 (2)	15 (4)
Trametinib	3 (< 1)	13 (4)

The updated OS analysis may also be impacted by crossover since patients in the vemurafenib arm were allowed to crossover to receive combination therapy after the study was stopped early for efficacy in July 2014 (21/352 [6%] of patients randomised to vemurafenib subsequently switched to received trametinib + dabrafenib). The methodologies employed to adjust for the effect of the crossover are discussed in Section 4.4.3.2 and the results are presented in section 4.7.5 (Table 48).

4.7.2.1 Combi-v Secondary endpoints

Progression-free survival

Investigator-assessed PFS was significantly longer in the in the combination group than in the vemurafenib group at both the interim and updated analyses (Table 37, Figure 15). Sensitivity analyses for PFS conducted at the time of the interim analysis were consistent with the ITT analysis (HRs in the range 0.53 to 0.57).[19; 20]

Table 37: Investigator-assessed PFS in COMBI-v (ITT population)

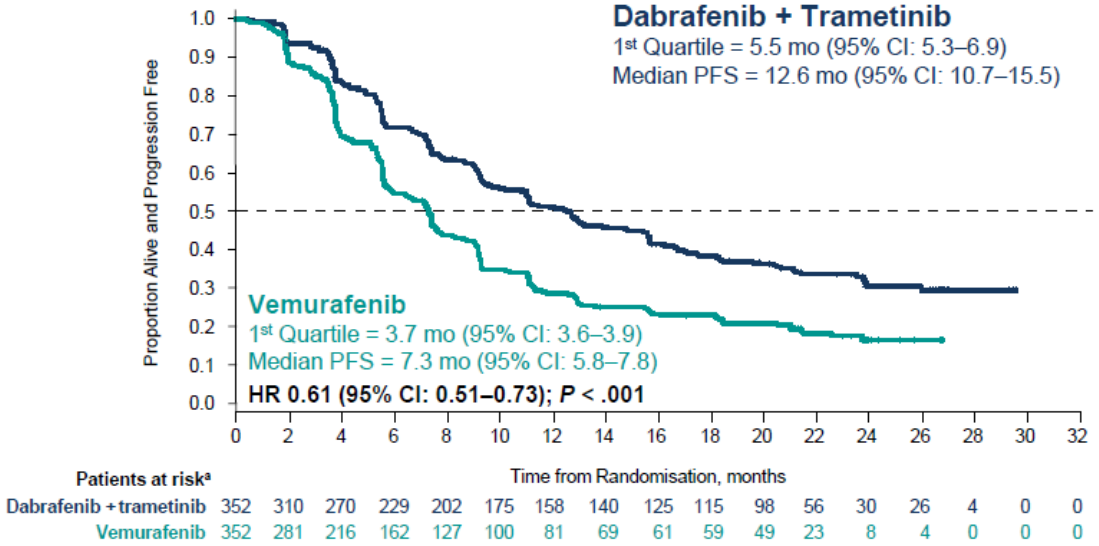
	17 April 2014 cut-off[19]		**13 March 2015 cut-off[20]**	
	Trametinib + dabrafenib N=352	**Vemurafenib monotherapy N=352**	**Trametinib + dabrafenib N=352**	**Vemurafenib monotherapy N=352**
Patient classification, n (%)				
Progressed or died (event)	166 (47)	217 (62)	214 (61)	246 (70)
Censored, follow-up ended	24 (7)	52 (15)	30 (9)	58 (16)
Censored, follow-up ongoing	162 (46)	83 (24)	108 (31)	48 (14)
Estimates for PFS, months[a]				
1st quartile (95% CI)	5.5 (5.3, 6.8)	3.7 (3.6, 3.9)	5.5 (5.3, 6.9)	3.7 (3.6, 3.9)
Median (95% CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)	12.6 (10.7, 15.5)	7.3 (5.8, 7.8)
3rd quartile (95% CI)	NR (16.1, NR)	12.9 (11.2, NR)	NR (23.9, NR)	13.6 (11.2, 21.0)
Adjusted hazard ratio[b]				
Estimate (95% CI)	0.56 (0.46, 0.69)		0.61 (0.51, 0.73)	
Stratified log rank p-value[b]	p<0.001		p<0.001	

a. Quartiles were estimated using the Brookmeyer Crowley method.

b. Hazard ratios are estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with trametinib + dabrafenib compared with monotherapy. Hazard ratio and p-value from stratified log-rank test are adjusted for randomised strata: baseline LDH and BRAF mutation status.

NA = Not available; NR = Not reached.

Figure 15: Kaplan-Meier Curves for PFS in COMBI-v (ITT population, March 2015 cut-off) [20]



Overall response rate (ORR) and duration of response

The investigator-assessed confirmed ORR was significantly higher in the trametinib + dabrafenib combination arm compared with the vemurafenib monotherapy arm at both the initial and updated cut-offs. More patients had a complete response in the trametinib + dabrafenib group compared with the vemurafenib group and the median duration of response was longer (Table 38).[19; 20]

Table 38: Investigator-assessed responses in COMBI-v (ITT population)

	17 April 2014 cut-off[19]		**13 March 2015 cut-off[20]**	
	Trametinib + dabrafenib N=352	**Vemurafenib monotherapy N=212**	**Trametinib + dabrafenib N=352**	**Vemurafenib monotherapy N=352**
Best response, n (%)				
CR	47 (13)	27 (8)	59 (17)	36 (10)
PR	179 (51)	153 (44)	172 (49)	150 (43)
SD	92 (26)	106 (30)	87 (25)	102 (29)
PD	22 (6)	38 (11)	22 (6)	39 (11)
NE	11 (3)	26 (7)	12 (3)	25 (7)
ORR, n (%)				
CR + PR	226 (64)	180 (51)	231 (66)	186 (53)
95% CI	(59.1, 69.4)	(46.1, 56.8)	(60.4, 70.6)	(47.5, 58.2)
Difference in ORR				
Difference	13		13	
95% CI	(5.7, 20.2)		(5.3, 20.2)	
p-value[a]	p=0.0005		p=0.0008	
Duration of response, months				
	n=226	**n=180**	**n=231**	**n=186**
Median	13.8	7.5	13.8	8.5
95% CI	(11.0, NR)	(7.3, 9.3)	(11.2, 18.1)	(7.4, 9.7)

a. Chi-squared test was used to calculate the p-value.

4.7.2.3 COMBI-v Health-related quality of life (HRQoL)

The HRQoL data for COMBI-v presented in the submission relate to the 17 April 2014 cut-off for the interim OS analysis, consistent with the HRQoL data used in the economic model.

HRQoL data were collected using the European Organisation for Research and Treatment of Cancer quality of life (EORTC QLQ-C30), EuroQoL-5D (EQ-5D), and Melanoma Subscale of the Functional Assessment of Cancer Therapy—Melanoma (FACT-M) questionnaires.

Completion of all questionnaires as a percentage of available patients for both treatment groups was >95% at baseline, >80% at all assessments until week 56, and >70% at the disease progression visit.

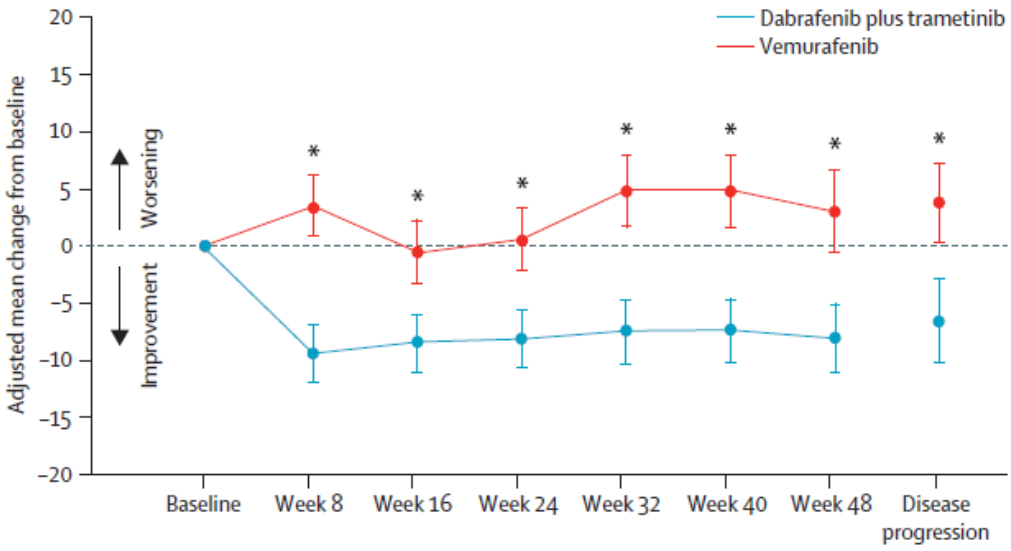
<u>European Organisation for Research and Treatment of Cancer Quality of Life C-30 Questionnaire (EORTC-QLQ-C30)</u>

Patients in both treatment arms reported similar global health status, functional, and symptom-related HRQoL scores at baseline, with differences not exceeding 4 points across any of the dimensions.[29]

Global health status

Mean global health status score was significantly better ($p<0.05$) and clinically meaningful (5.2- to 7.9-point ["small"] improvement) for patients receiving trametinib + dabrafenib compared with those on vemurafenib at weeks 8, 16, 24, 32, 40, 48 and at disease progression (Figure 16).[29]

Figure 16: Change from baseline in Global Health Status in COMBI-v (ITT population, April 2014) [29]



Patients with data (n)	Baseline	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	Disease progression
Dabrafenib + trametinib	327	321	303	268	231	189	148	122
Vemurafenib	312	314	247	202	161	121	88	165

Functional dimensions

With regard to the functional domains of the EORTC-QLQ-C30, differences in mean scores for physical, role, and social functioning were statistically significant (p<0.05) and clinically meaningful (as defined by the minimally important differences [MCIDs]), in favour of the trametinib + dabrafenib over vemurafenib monotherapy at weeks 8 to 48, and at disease progression (small to-moderate MCIDs: 5·6–9·2 point improvement for physical functioning; 7·4–14·7 point improvement for role functioning, and 8·5–11·8 point improvement for social functioning). Differences in mean emotional functioning scores were statistically significant (p<0·05) and clinically meaningful in favour of the combination over vemurafenib at weeks 16, 32, 48, and at disease progression. Mean cognitive functioning scores were slightly below baseline at all assessments for both treatment arms, with statistically significant differences only at weeks 8, 16, 32, and at disease progression in favour of the combination therapy (Table 39).[29]

Table 39: Summary of EORTC QLQ-C30 functional domain scores in COMBI-v (ITT population, April 2014 cut-off) 29

Functional Domain	Difference[a] (95% CI)						
	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	PD
Physical functioning	6.49[b] (4.02, 8.97)[c]	6.27[b] (3.71, 8.83)[c]	5.61[b] (2.82, 8.40)[c]	7.08[b] (4.04, 10.11)[c]	7.90[b] (4.98, 10.82)[c]	8.74[b] (5.15, 12.32)[c]	9.15[b] (5.71, 12.59)[c]
Role functioning	10.00[b] (6.08, 13.93)[c]	7.44[b] (3.32, 11.57)[c]	8.96[b] (4.81, 13.11)[c]	12.61[b] (8.15, 17.08)[c]	9.93[b] (5.08, 14.78)[c]	14.68[b] (9.35, 20.01)[c]	13.60[b] (8.50, 18.71)[c]
Emotional functioning	4.15[b] (1.34, 6.96)[c]	5.36[b] (2.43, 8.28)[c]	4.95 (1.76, 8.14)[c]	6.19[b] (2.85, 9.54)[c]	4.46[b] (1.00, 7.92)[c]	6.33[b] (2.46, 10.21)[c]	6.32[b] (2.61, 10.03)[c]
Cognitive functioning	3.53 (1.03, 6.03)[c]	2.82 (0.16, 5.48)[c]	2.28 (-0.62, 5.17)	3.27 (0.16, 6.38)[c]	2.24 (-1.17, 5.66)	3.22 (-0.47, 6.91)	5.44[b] (2.12, 8.75)[c]
Social functioning	9.91[b] (6.25, 13.57)[c]	9.20[b] (5.36, 13.04)[c]	8.48[b] (4.57, 12.40)[c]	11.81[b] (7.84, 15.78)[c]	11.12[b] (7.02, 15.22)[c]	9.73[b] (5.20, 14.26)[c]	10.09[b] (5.58, 14.60)[c]

[a] Difference in change from baseline scores for dabrafenib + trametinib vs vemurafenib; [b] Clinically meaningful difference; [c] Statistically significant ($P < .05$).

Difference in scores favours dabrafenib + trametinib

Symptom dimensions

For symptom-related dimensions of the EORTC-QLQ-C30, differences in mean scores for pain, insomnia, appetite loss and diarrhoea were statistically significant (p<0.05) and clinically meaningful in favour of patients receiving trametinib + dabrafenib compared with those receiving vemurafenib monotherapy for all assessment points. Fatigue scores were also statistically significant and clinically meaningful in favour of the combination at all time points, with the exception of week 24 when the difference in the mean score between treatment arms did not quite reach the MCID. For the other symptom dimensions (nausea and vomiting, dyspnoea, and financial difficulties), differences between arms trended in favour of combination therapy. However, for constipation, the mean scores were lower during treatment than at baseline for both groups (Table 40).[29]

Table 40: Summary of EORTC QLQ-C30 symptom domain scores in COMBI-v (ITT population, April 2014 cut-off) [29]

Symptom Domain	Difference[a] (95% CI)						
	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	PD
Pain	-13.20[b] (-16.86, -9.54)[c]	-8.05[b] (-11.78, -4.32)[c]	-8.82[b] (-12.56, -5.07)[c]	-12.60[b] (-16.91, -8.46)[c]	-12.46[b] (-16.69, -8.23)[c]	-11.41[b] (-16.21, -6.61)[c]	-10.57[b] (-15.63, -5.51)[c]
Fatigue	-9.85[b] (-13.40, -6.31)[c]	-6.18[b] (-9.81, -2.55)[c]	-4.25 (-8.11, -0.40)[c]	-8.05[b] (-12.21, -3.90)[c]	-8.05[b] (-12.33, -3.76)[c]	-9.29[b] (-14.47, -4.11)[c]	-8.27[b] (-12.83, -3.72)[c]
Nausea and vomiting	-5.33[b] (-8.20, -2.45)[c]	-2.38 (-5.22, 0.45)	-1.62 (-4.46, 1.22)	-4.17 (-6.96, -1.38)[c]	-2.01 (-4.75, 0.73)	-0.21 (-3.01, 2.59)	-4.12 (-7.39, -0.86)[c]
Dsypnoea	-2.94 (-6.11, 0.23)	0.65 (-2.63, 3.94)	-1.76 (-4.88, 1.35)	0.59 (-3.03, 4.22)	-1.21 (-5.00, 2.58)	-2.68 (-7.22, 1.86)	-3.39 (-7.47, 0.69)
Insomnia	-11.19[b] (-15.24, -7.15)[c]	-6.62[b] (-10.84, -2.41)[c]	-7.25[b] (-11.37, -3.13)[c]	-11.19[b] (-15.96, -6.42)[c]	-11.99[b] (-16.41, -7.57)[c]	-13.78[b] (-18.99, -8.57)[c]	-10.53[b] (-15.19, -5.86)[c]
Appetite loss	-14.26[b] (-18.31, -10.20)[c]	-10.38[b] (-14.81, -5.95)[c]	-10.75[b] (-14.93, -6.57)[c]	-8.92[b] (-13.45, -4.38)[c]	-7.43[b] (-11.93, -2.93)[c]	-7.44[b] (-12.37, -2.52)[c]	-11.90[b] (-16.88, -6.92)[c]
Constipation	3.46 (0.48, 6.44)[c]	4.15 (0.90, 7.40)[c]	3.07 (-0.18, 66.33)	4.32 (1.00, 7.64)[c]	3.67 (0.21, 7.12)[c]	3.84 (-0.28, 7.95)	0.54 (-2.92, 4.00)
Diarrhoea	-8.82[b] (-12.42, -5.21)[c]	-13.87[b] (-17.89, -9.85)[c]	-16.08[b] (-20.17, -11.98)[c]	-16.19[b] (-20.30, -12.09)[c]	-13.74[b] (-18.66, -8.82)[c]	-16.76[b] (-21.44, -12.08)[c]	-11.24[b] (-16.11, -6.37)[c]
Financial difficulties	-3.12 (-6.79, 0.55)	-1.06 (-5.01, 2.88)	-0.55 (-4.58, 3.48)	-3.53 (-7.53, 0.47)	-6.18[b] (-10.56, -1.80)[c]	-3.65 (-8.14, 0.84)	-2.99 (-7.22, 1.23)

[a] Difference in change from baseline scores for dabrafenib + trametinib vs vemurafenib
[b] Clinically meaningful difference; [c] Statistically significant ($P < .05$).

Difference in scores favours dabrafenib + trametinib
Difference in scores favours vemurafenib

EuroQoL-5D questionnaire (EQ-5D)

Mean baseline EQ-5D thermometer scores were comparable in both treatment groups (68·3 for combination therapy vs 68·8 for vemurafenib, respectively). Health utility scores were also similar between the treatment arms at baseline (0.751 and 0.715 for combination therapy and vemurafenib, respectively).

Thermometer and utility scores

Among patients receiving trametinib + dabrafenib therapy, adjusted mean thermometer and utility scores increased (i.e. improved) relative to baseline for weeks 8, 16, 24, 32, 40, 48, and at disease progression, whereas for patients receiving vemurafenib, scores decreased (were worse) for the corresponding visits. When assessed for differences between treatment groups using mixed-model repeated measures analyses, mean thermometer and health utility scores were significantly better (p<0·05) and clinically meaningful (6·8–11.5 and 0·08–0·11 points, respectively) for the combination compared with vemurafenib for all assessments (Table 41).[29]

Table 41: Summary of Thermometer and Utility Scores for EQ-5D in COMBI-v (ITT Population, April 2014 cut-off) [29]

	Change from Baseline to	Dabrafenib + Trametinib (N=352)		Vemurafenib (N=352)		Diff. vs. Vemurafenib	95% CI for Diff	P-value for Diff.
		n	Adjusted Mean	n	Adjusted Mean			
Thermometer score	Week 8	306	4.99	302	-2.97	7.96	(5.14, 10.79)	<0.001
	Week 16	286	5.99	232	-2.06	8.05	(5.06, 11.04)	<0.001
	Week 24	254	4.23	195	-2.61	6.83	(3.82, 9.85)	<0.001
	Week 32	217	8.68	159	-2.85	11.53	(3.29, 19.76)	0.006
	Week 40	179	4.91	117	-2.51	7.41	(3.96, 10.87)	<0.001
	Week 48	141	6.39	87	-2.69	9.08	(4.96, 13.20)	<0.001
	At PD	118	4.84	156	-5.67	10.51	(6.79, 14.23)	<0.001
Utility score	Week 8	307	0.08	302	-0.01	0.09	(0.06, 0.12)	<0.001
	Week 16	286	0.08	235	0.00	0.09	(0.05, 0.12)	<0.001
	Week 24	255	0.07	191	-0.02	0.08	(0.05, 0.12)	<0.001
	Week 32	218	0.06	157	-0.05	0.10	(0.06, 0.14)	<0.001
	Week 40	179	0.07	116	-0.04	0.11	(0.07, 0.15)	<0.001
	Week 48	139	0.07	85	-0.04	0.11	(0.06, 0.15)	<0.001
	At PD	115	0.06	154	-0.05	0.11	(0.06, 0.16)	<0.001

Summary of Mixed-Model Repeated Measures Analysis for Change from Baseline in Thermometer and Utility Scores for EQ-5D.

FACT-M Melanoma Subscale

Mean baseline FACT-M Melanoma Subscale scores were similar between the combination and the vemurafenib arms (53·1 vs. 51·7). Relative to baseline, adjusted mean FACT-M melanoma subscale scores increased (improved) for trametinib + dabrafenib for weeks 8 through to 48 and at disease progression, and decreased (worsened) for vemurafenib at the corresponding visits. Differences in scores between the treatment arms were significantly better (p<0.001) and clinically meaningful (2.5- to 3.7-point difference) in favour of trametinib + dabrafenib over vemurafenib monotherapy at all assessments (Table 42).[29]

Table 42: Summary of FACT-M Melanoma Subscale Scores in COMBI-v (ITT Population, April 2014 cut-off) [29]

Change from Baseline to	Dabrafenib + Trametinib (N=352)		Vemurafenib (N=352)		Diff. vs. Vemurafenib	95% CI for Diff	P-value for Diff.
	n	Adjusted Mean	n	Adjusted Mean			
Week 8	308	1.61	300	-2.01	3.62	(2.54, 4.71)	<0.001
Week 16	289	1.96	234	-0.97	2.93	(1.81, 4.05)	<0.001
Week 24	257	1.65	196	-0.81	2.45	(1.32, 3.58)	<0.001
Week 32	219	2.10	154	-1.29	3.39	(2.23, 4.55)	<0.001
Week 40	180	2.03	115	-0.82	2.85	(1.67, 4.03)	<0.001
Week 48	139	1.98	85	-1.02	3.00	(1.52, 4.48)	<0.001
At PD	119	1.93	157	-1.75	3.68	(2.39, 4.96)	<0.001

Summary of Mixed-Model Repeated Measures Analysis for Change from Baseline in Thermometer and Utility Scores for EQ-5D.

Summary of HRQoL assessments in COMBI-v

The HRQoL analyses in COMBI-v demonstrate that the combination of trametinib + dabrafenib provides statistically significant and clinically meaningful improvements in many aspects of HRQoL over vemurafenib monotherapy. The findings confirm that the efficacy superiority of the combination in terms of PFS and OS together with its AE profile translate into substantial HRQoL benefits as perceived by the patient.[29]

4.7.3 BRF113220 (Part C)

Efficacy results presented for the BRF113220 (Part C) study focus on the combination of dabrafenib 150mg b.d. plus trametinib 2mg o.d. (combination 150/2) as this is the licensed dosage for the combination, and the dabrafenib monotherapy arms. Results for the dabrafenib 150mg plus trametinib 1mg o.d. arm (combination 150/1) can be found in the Clinical Study Report[114] and the relevant publications.[25]

4.7.3.1 BRF113220 Primary endpoints

Progression-free survival

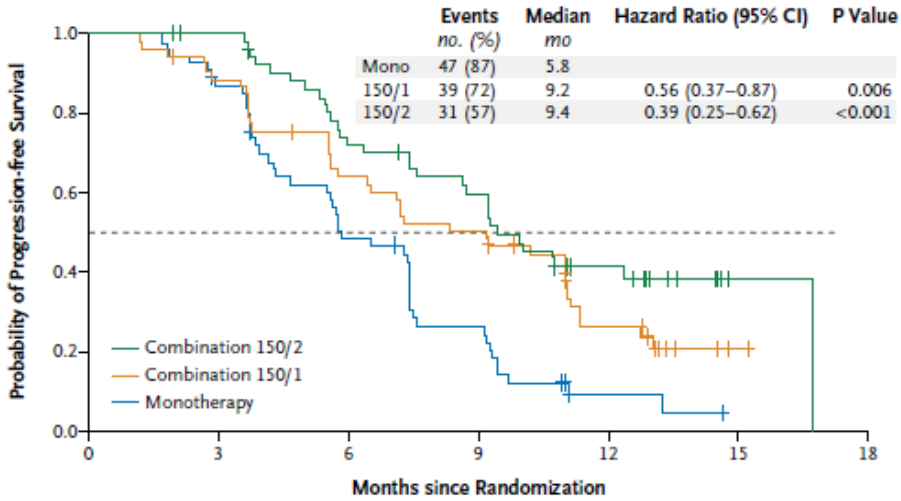
At the time of the pre-specified efficacy analysis (31 May 2012 cut-off), median PFS as assessed by the investigators was significantly longer in the combination 150/2 arm than the dabrafenib monotherapy arm (Table 43). A Kaplan-Meier estimate of PFS rate at 12 months showed that a larger proportion of patients were progression-free on combination 150/2 than on dabrafenib monotherapy (41% vs. 9%) (Figure 17).[25]

Table 43: PFS in BRF113220 by investigator assessment (ITT population, May 2012 cut-off)[25]

	Treatment arms	
	Trametinib + dabrafenib 150/2 N=52	**Dabrafenib monotherapy N=54**
Subject classification, n (%)		
Progressed or died (event)	31 (57)	47 (87)
Censored, follow-up ended	3 (6)	1 (2)
Censored, follow-up ongoing	20 (37)	6 (11)
Kaplan-Meier estimates for PFS, months[a]		
1st quartile (95% CI)	5.8 (5.3, 8.7)	3.8 (3.6, 5.5)
Median (95% CI)	9.4 (8.6, 16.7)	5.8 (4.6, 7.4)
3rd quartile (95% CI)	16.7 (12.4, 16.7)	9.1 (7.4, 9.4)
Hazard ratio[b]		
Estimate (95% CI)	0.39 (0.25, 0.62)	
Stratified Log rank p-value[c]	<0.0001	

a. Confidence intervals were estimated using the Brookmeyer Crowley method.
b. Hazard ratio estimated using Pike estimator. A hazard ratio <1 indicates a lower risk with combination compared with monotherapy.
c. P-values are based on 2-sided log rank test. The censoring method included censoring for extended loss to follow-up, new anti-cancer therapy, and excluding symptomatic progression.

Figure 17: Kaplan-Meier Curves for investigator-assessed PFS in BRF113220 (ITT population, May 2012 cut-off) [25]



No. at Risk						
Monotherapy	54	46	25	13	2	0
Combination 150/1	54	47	33	26	11	1
Combination 150/2	54	52	36	29	15	1

Sensitivity analyses

PFS sensitivity analyses conducted to address the potential for evaluation bias were generally consistent with the primary investigator-assessed PFS analysis for the combination 150/2 group (HRs in the range 0.39 to 0.41). The improvement in PFS as assessed by a blinded independent review committee (BIRC) was less pronounced (HR 0.55 [95% CI: 0.33, 0.93]; p=0.02). This difference is largely attributable to an imbalance in informative censoring, most commonly in cases in which new lesions were identified at the study centre but were not considered to constitute definitive progression on central review. Less censoring occurred in the combination 150/2 group, in part because of additional follow-up beyond investigator-assessed progression. Such follow-up did not occur for patients who had disease progression while receiving monotherapy; these patients crossed over to receive combination therapy and could no longer be evaluated for disease progression under their originally assigned therapy.[25]

At a *post hoc* PFS analysis based on 15 January 2014 cut-off (median follow-up time 34 months), median PFS was 9.4 months in the combination 150/2 group versus 5.8 months in the monotherapy group (HR 0.41 [95% CI 0.27-0.64]; p<0.0001).[117]

<u>Overall response rate (ORR) and duration of response</u>

A significantly higher confirmed ORR was observed in the combination 150/2 group compared with the dabrafenib monotherapy group (76% vs. 54%; p=0.0264) (Table 44).[25] No patient in the combination 150/2 arm had progressive disease (PD) as the best outcome at the time of the analysis. The median duration of response based on investigator assessment was 10.5 months in the combination 150/2 arm versus 5.6 months in the dabrafenib monotherapy arm (Table 44). At the time of analysis, 46% of responding patients in the

combination 150/2 arm were still receiving study treatment compared with 14% of responding patients in the dabrafenib monotherapy arm.[114]

Table 44: Investigator-assessed responses in BRF113220 (Part) (ITT population, May 2012 cut-off)[25]

	Treatment arms	
	Trametinib + dabrafenib 150/2 N=54	**Dabrafenib monotherapy N=54**
Best response, n (%)		
CR	5 (9)	2 (4)
PR	36 (67)	27 (50)
SD	13 (24)	22 (41)
PD	0	3 (6)
NE	0	0
ORR, n (%)		
CR+PR	41 (76)	29 (54)
95% CI[a]	62.4, 86.5	39.6, 67.4
Difference in ORR		
Difference	22%	
95% CI[a]	2.5, 40.7	
p-value[a]	0.0264	
Duration of response, months[b]		
1st quartile (95% CI)	6.3 (3.7, 8.1)	3.9 (3.7, 5.5)
Median (95% CI)	10.5 (7.4, 14.9)	5.6 (4.5, 7.4)
3rd quartile (95% CI)	14.9 (-, -)	7.6 (5.6, 11.3)

a. CIs were estimated using the Brookmeyer Crowley method.

b. p-values and 95% CIs were calculated based on the unconditional exact method.

4.7.3.2 BRF113220 Secondary endpoints

Overall survival

Median overall survival (OS) was not reached at the time of the initial analysis (31 May 2012 cut-off). The percentage of patients who were alive at 12 months was 79% in the combination 150/2 group and 70% in the monotherapy group, though 80% of patients randomised to monotherapy arm had crossed over to receive combination 150/2 therapy at this time point (Table 45).[25]

Table 45: Overall survival in BRF113220 (Part C) (ITT population, May 2012 cut-off) [25]

	Treatment arms	
	Trametinib + dabrafenib 150/2 N=54	**Dabrafenib Monotherapy N=54**
Subject classification, n (%)		
Died (event)	14 (26)	19 (35)
Censored, follow-up ended	0	0
Censored, follow-up ongoing	40 (74)	35 (65)
Kaplan-Meier estimates for overall survival, months[a]		
1st quartile (95% CI)	12.7 (9.6, NR)	10.7 (7.9, 13.4)
Median (95% CI)	NR (NR, NR)	NR (13.4, NR)

3rd quartile (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio[b]		
Estimate (95% CI)	0.67 (0.34, 1.34)	
Log rank p-value	0.2591	
Estimated survival at 12 months, %		
Rate (95% CI)	79 (66, 88)	70 (55, 80)

a. Confidence intervals were estimated using the Brookmeyer Crowley method.

b. Hazard ratios were estimated using the Pike estimator. A HR <1 indicates lower risk with this treatment compared with the monotherapy arm.

NR = Not reached.

Updated OS analyses have been conducted based on cut-off dates of 29 March 2013, 15 January 2014 and 15 January 2015, as part of regular landmark analyses (Table 46).

Table 46: Survival data summaries from the primary and *post hoc* analyses in BRF113220 (ITT population) [25; 26; 115; 117]

Cut-off dates	Follow-up time (median, months)	Treatment	Number of deaths n (%)	Median OS, months (95% CI[a])	Hazard ratio[b] (95% CI)
31 May 2012 (primary)[25]	14 months	Combination 150/2	14 (26)	NR (NR, NR)	0.67 (0.34, 1.34)
		Dabrafenib monotherapy	19 (35)	NR (13.4, NR)	
29 March 2013[115]	24 months	Combination 150/2	25 (46)	23.8 (17.5, NR)	0.73 (0.43, 1.24)
		Dabrafenib monotherapy	31 (57)	20.2 (14.5, 25.9)	
15 January 2014[117]	34 months	Combination 150/2	36 (67)	25.0 (17.5, NR)	0.79 (0.49, 1.27)
		Dabrafenib monotherapy	32 (59)	20.2 14.5, 27.1)	
15 January 2015[26]	46 months	Combination 150/2	36 (67)	25.0 (17.5, 36.5)	0.77 (0.49, 1.21)
		Dabrafenib monotherapy	41 (76)	20.2 (14.5, 27.1)	

a. Confidence intervals were estimated using the Brookmeyer Crowley method.

b. Hazard ratios were estimated using the Pike estimator. A HR <1 indicates lower risk with this treatment compared with the monotherapy arm.

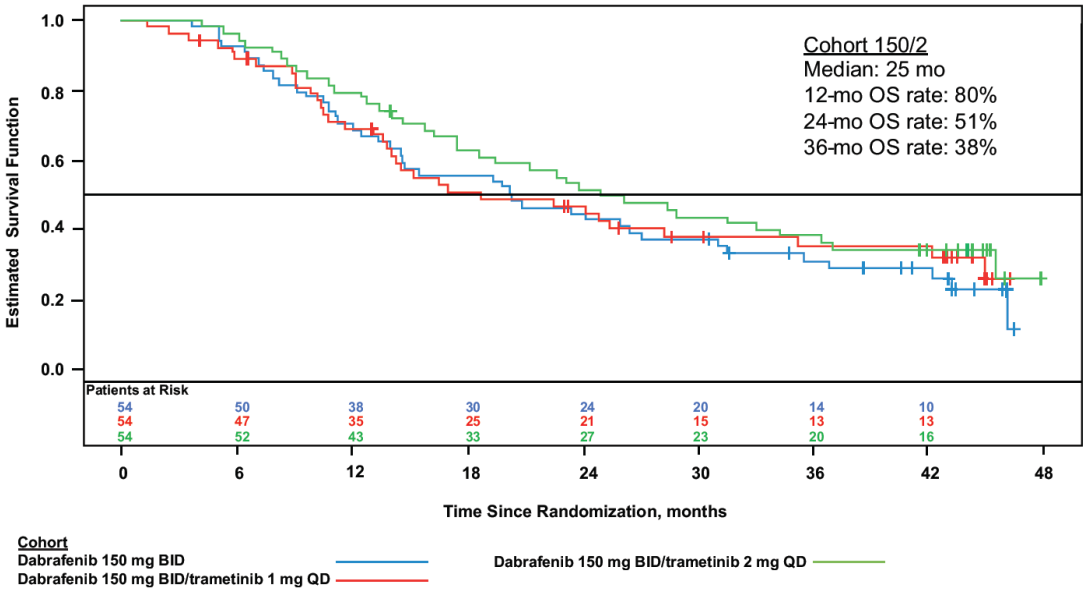
NR = Not reported

The results of the latest analysis suggest that the improvements in OS achieved with trametinib + dabrafenib combination 150/2 therapy versus dabrafenib monotherapy are maintained over 3 years of treatment (Table 47 and Figure 18). Although the difference between the two arms was not statistically significant (HR 0.77 [95% CI; 0.49, 1.21]), there was a trend in favour of combination 150/2 therapy. It should also be noted that, by this time, 83% of the dabrafenib monotherapy population had crossed over to receive combination 150/2 therapy following disease progression which has likely confounded OS in the monotherapy arm. Results of analyses conducted to adjust for the effect of this crossover are presented in section 4.7.5. Furthermore, OS rates at 1 year, 2 years, and 3 years were all higher in the combination 150/2 arm than in the dabrafenib monotherapy arm (Table 47).[26]

Table 47: Updated overall survival rates in BRF113220 (Part C) (ITT population, January 2015 cut-off) [26]

	Treatment arms	
	Trametinib + dabrafenib 150/2 N=54	**Dabrafenib monotherapy N=54**
OS rate, %		
Year 1	80	70
Year 2	51	44
Year 3	38	31

Figure 18: Kaplan-Meier updated overall survival curves in BRF113220 (Part C) (ITT population, January 2015 cut-off) [26]



4.7.4.1 Health-related quality of life

HRQoL data were not collected in the BRF113220 study.

4.7.5 Results of OS adjustment analyses

Results for all adjustments undertaken to account for crossover in the COMBI-v and BRF113220 (Part C) studies, based on the latest data cuts, are presented in Table 48.

For reasons discussed earlier (section 4.4.3.2), the RPSFTM 'treatment group' analysis with re-censoring is believed to provide the most clinically plausible estimate of treatment effect on OS in the COMBI-v study in the absence of treatment switching; this yields an adjusted HR of 0.63 (95% CI: 0.50, 0.79) for trametinib + dabrafenib combination therapy versus vemurafenib monotherapy. The counterfactual OS data for the vemurafenib arm (i.e. the adjusted OS data representing the survival times that would have been observed in the absence of treatment switching) generated using this methodology have been incorporated in the economic modelling.[27]

Likewise, the RPSFTM 'treatment group' method appears to have produced the most appropriate estimate of the treatment effect that would have been observed in the BRF113220 study in the absence of switching. This analysis generated an adjusted OS HR of 0.55 (95% CI: 0.20, 1.55). The estimate is not affected by whether or not re-censoring is incorporated. The confidence intervals are wide, in part due to the RPSFTM method, and in part relating to the small sample size of the underlying study.[118]

Taken together, the results of all these analyses strongly indicate that trametinib + dabrafenib combination therapy is associated with a clinically relevant reduction in the risk of death versus BRAF inhibitor monotherapy.

Table 48: Results (HR, 95% CI) of comprehensive crossover adjustments for COMBI-v and BRF113220 OS data

Method type	Description	COMBI-v (MEK116513)[27]	BRF113220 (Part C)[118]
		January 2015	January 2015
1. ITT	Intention to treat analysis (to provide a 'baseline' analysis)	0.65* (0.53, 0.81)	0.77 (0.49, 1.21)
2. Naive	Censor crossover patients at time of crossover	0.65 (0.52, 0.80)	0.75 (0.31, 1.78)
3. Naive	Exclude crossover patients	0.59 (0.48, 0.74	1.42 (0.58, 3.45)
4. Complex	RPSFT 'treatment group' analysis. This estimates an average treatment effect of being allocated to the experimental group, adjusted for crossover.	0.63 (0.50, 0.79)	0.55 (0.20, 1.55)
5. Complex	RPSFT 'on treatment' analysis. This estimates the average treatment effect of full treatment (no discontinuation) compared to no treatment.	0.62 (0.49, 0.78)	0.60 (0.25, 1.45)

6. Complex	IPCW. This censors patients at point of crossover and weights remaining observations based upon baseline and time-dependent covariates	0.61 (0.48, 0.78)	Not conducted
7. Complex	IPE Algorithm 'treatment group' analysis. This estimates an average treatment effect of being allocated to the experimental group, adjusted for crossover.	Not conducted	0.19 (0.01, 3.36)
8. Complex	IPE Algorithm 'on treatment' analysis. This estimates the average treatment effect of full treatment (no discontinuation) compared to no treatment.	Not conducted	0.51 (0.16, 1.64)
9. Complex	IPE Algorithm 'on treatment - observed' analysis. This estimates the average treatment effect of observed experimental treatment compared to no treatment, assuming an effect is only received while on treatment.	Not conducted	0.64 (0.29, 1.40)

Note: Results given to 2 decimal places. RPSFT = Rank Preserving Structural failure Time; IPE = Iterative Parameter Estimation; IPCW = Inverse Probability of Censoring Weights.

* ITT analysis results presented are from Cox proportional hazards models, stratified by BRAF status and baseline LDH. Novartis used a Pike Estimator to calculate hazard ratios, which resulted in an ITT HR of 0.66 (95% CI: 0.53, 0.81).

4.8. Subgroup analysis

This section should be read with the NICE guide to the methods of technology appraisal, sections 5.10.1–5.10.12.

4.8.1. Provide details of any subgroup analyses carried out. Specify the rationale and whether they were pre-planned or post-hoc.

Details of subgroups examined and analyses undertaken for the COMBI-d (MEK115306), COMBI-v (MEK116513) and BRF113220 (Part C) studies are described fully in Table 15 (bottom row). These analyses were conducted to investigate the consistency of the clinical benefits observed with trametinib + dabrafenib combination therapy compared with dabrafenib or vemurafenib as monotherapies.

Rationale for choice of subgroups

A number of independent prognostic factors have been identified in metastatic melanoma, which consequently formed the basis of the subgroups examined in the RCTs. These include the stage of advanced disease where patients with stage IV melanoma are sub-categorised; patients with M1a disease (metastasis to distant skin, subcutaneous tissues, and/or lymph nodes) have a relatively better prognosis compared to those with metastases at any other distant anatomic site. Patients with M1b disease (metastasis to the lungs) have an intermediate prognosis and patients with M1c disease (metastasis to any non-pulmonary visceral site) disease have the worst prognosis.[57] Serum level of LDH is also an adverse

prognostic marker and all patients with elevated LDH are assigned to the M1c category, regardless of site of distant metastasis.[57] Additionally, the number of distant metastases has been documented as an important prognostic factor in melanoma.[5; 57] Age and performance status of a patient are major prognostic factors predicting for survival in many cancers. However, gender is an interesting prognostic factor in melanoma. Being female has been associated with a survival advantage in a number of cancers and the female advantage has been found to be considerably higher in melanoma than other types of cancer.[143] Finally, different genotypes exist within BRAF-mutant metastatic melanoma where the V600E and V600K genotypes show different clinical behaviour: patients with the V600K mutation have been found to have a significantly shorter disease-free interval from diagnosis of primary melanoma to first distant metastasis than those with V600E mutations.[155]

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 characteristics of the participants within the subgroups explored in the subgroup analyses of the RCTs are as follows:

- BRAF V600 mutation (V600E or V600K)
- Age (<65 years or ≥65 years)
- Gender (male or female)
- Baseline LDH levels (≤ULN or >ULN)
- Baseline ECOG performance status (0 or ≥1)
- Disease stage at baseline (IIIcM0, IVM1a, IVM1b or IVM1c)
- Presence of visceral disease at baseline (absent or present)
- Number of disease sites at baseline (<3 or ≥3)
- Prior immunotherapy (yes or no)
- Brain metastases at baseline (absent or present) (BRF113220 only).

Whilst these are important known prognostic factors in metastatic melanoma as discussed in section 4.8.1, they are not directly relevant to the decision problem since the population under consideration for trametinib + dabrafenib combination therapy is for <u>all</u> adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

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

The subgroup analyses were performed with the use of an unstratified log-rank test to compare treatment arms within each subgroup. Kaplan-Meier quartile estimates were created for each treatment arm within the subgroup categories, and HRs were calculated within each subgroup category. Forest plots were also generated. No tests for interaction

have been performed and p-values are not available for any subgroup comparisons as the studies were not powered to demonstrate statistically significant differences within the subgroups.[17; 19]

4.8.4. Provide a summary of the results for the subgroups, with full details provided in an appendix.

COMBI-d

PFS and OS were significantly longer with trametinib + dabrafenib combination therapy than with dabrafenib monotherapy for every subgroup analysed. Forest plots for the subgroup analyses of PFS and OS in COMBI-d (as of the January 2015 cut-off) are presented in Figure 19 and Figure 20). All of the subgroup HRs favoured trametinib + dabrafenib combination therapy.[18] Subgroup analyses of ORR were also consistent with the results of the ITT analysis.[110]

Figure 19: Hazard ratios and 95% CI for PFS subgroup analyses in COMBI-d (ITT population, January 2015 cut-off) [18]

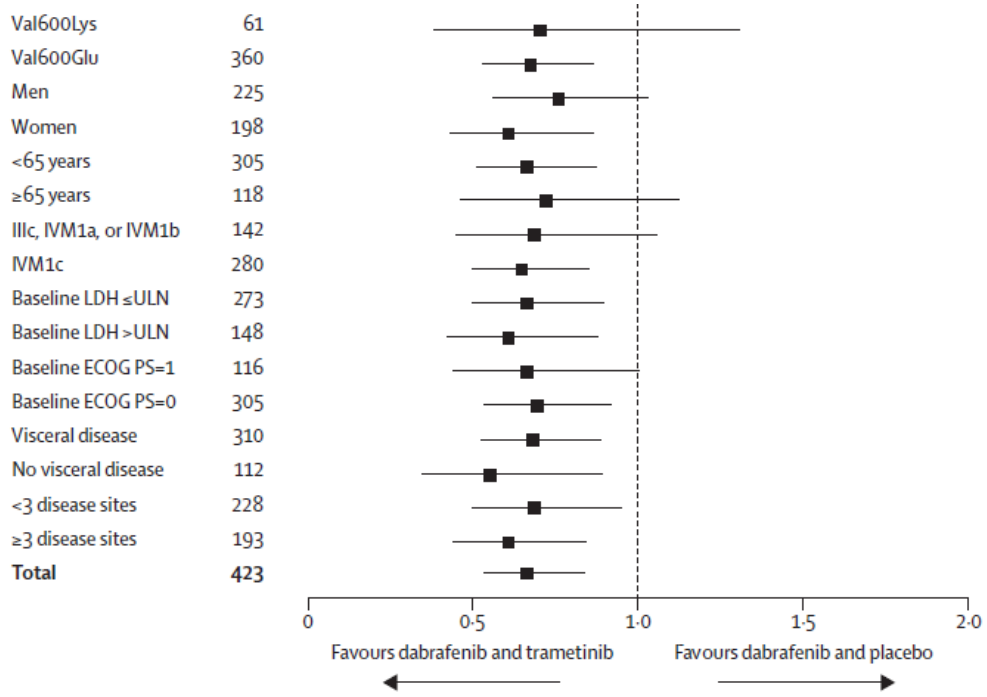
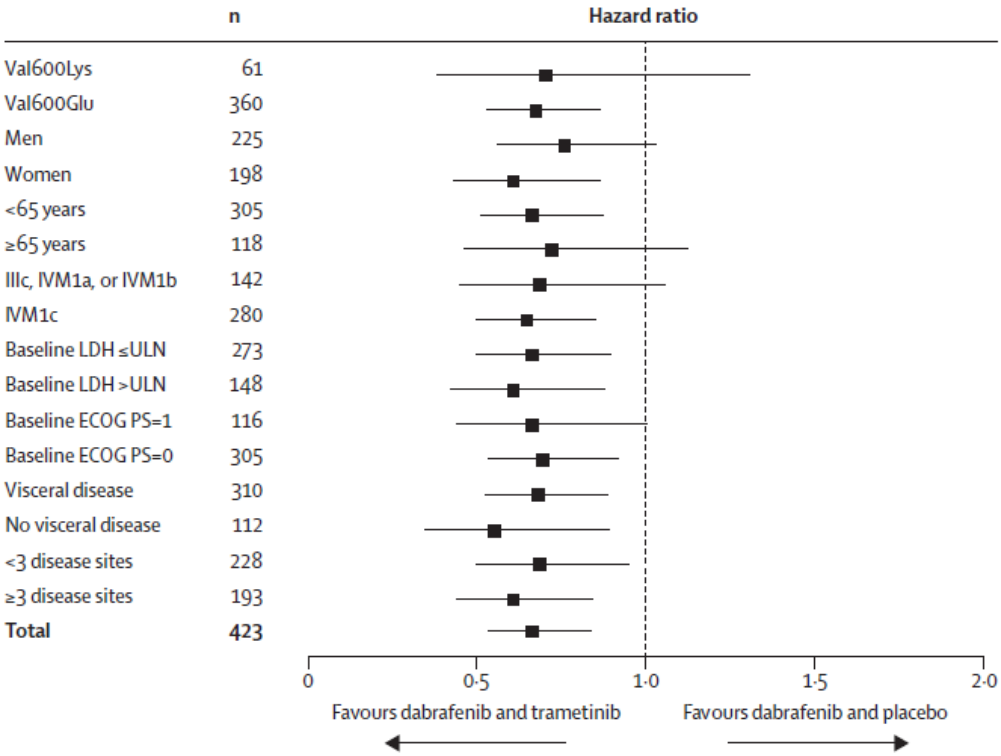


Figure 20: Hazard ratios and 95% CI for OS subgroup analyses in COMBI-d (ITT population, January 2015 cut-off) [18]



<u>COMBI-v</u>

Forest plots for the subgroup analyses of OS and PFS in COMBI-v are presented in Figure 21 and Figure 22 below. Again, all of the subgroup HRs favoured trametinib + dabrafenib combination therapy over vemurafenib monotherapy.[19; 20] Subgroup analyses of ORR were also consistent with the results of the ITT analysis.[113]

Figure 21: Hazard ratios and 95% CI for OS subgroup analyses in COMBI-v (ITT population, March 2015 cut-off) [20]

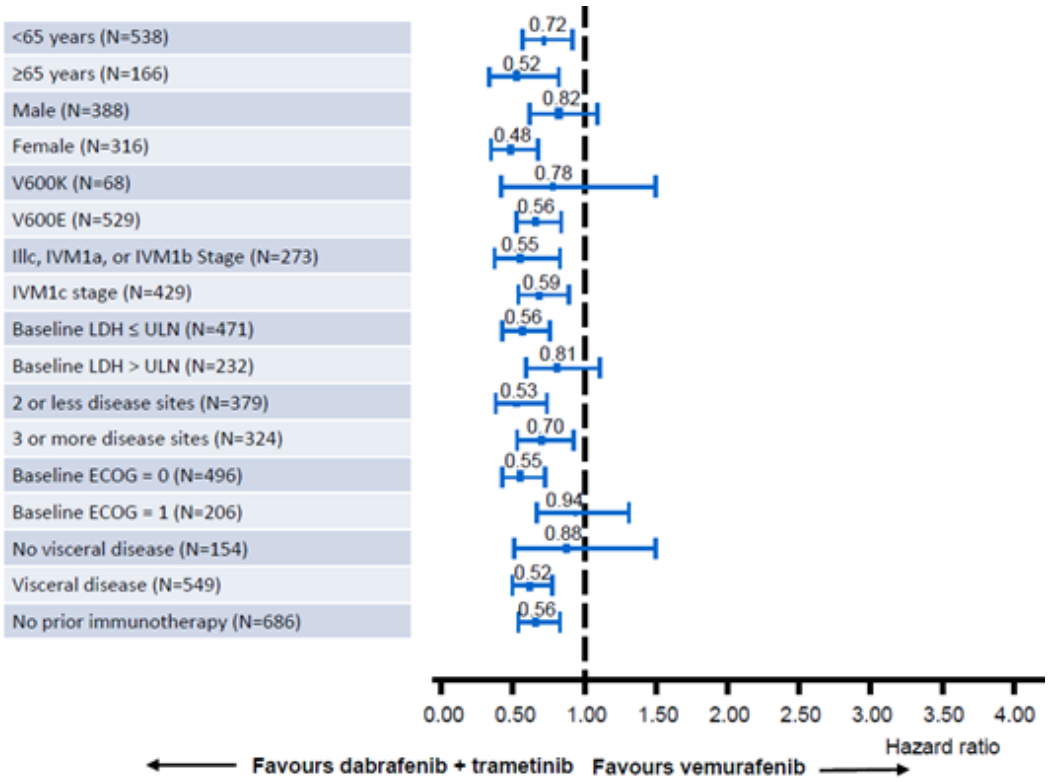
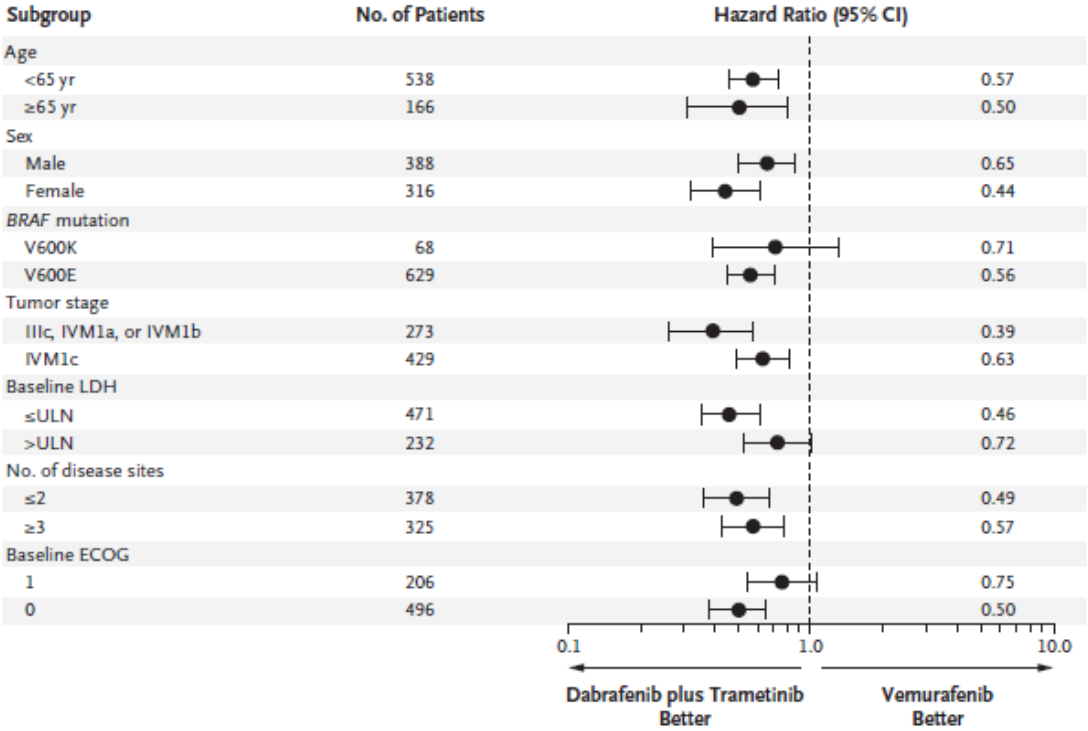


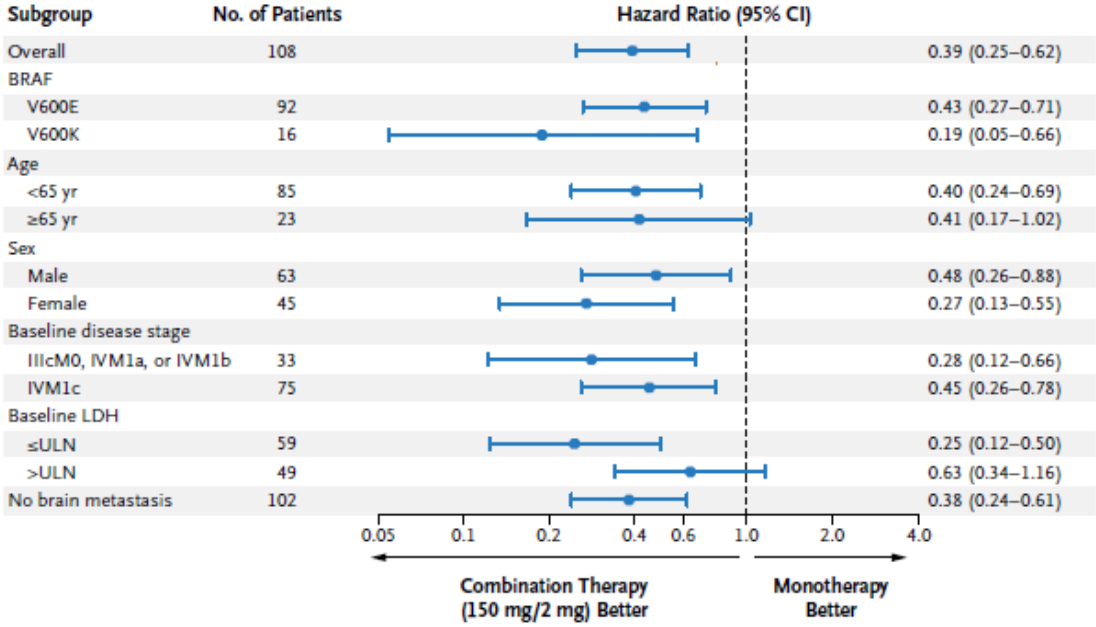
Figure 22: Hazard ratios and 95% CI for PFS subgroup analyses in COMBI-v (ITT population, April 2014 cut-off) [19]



BRF113220

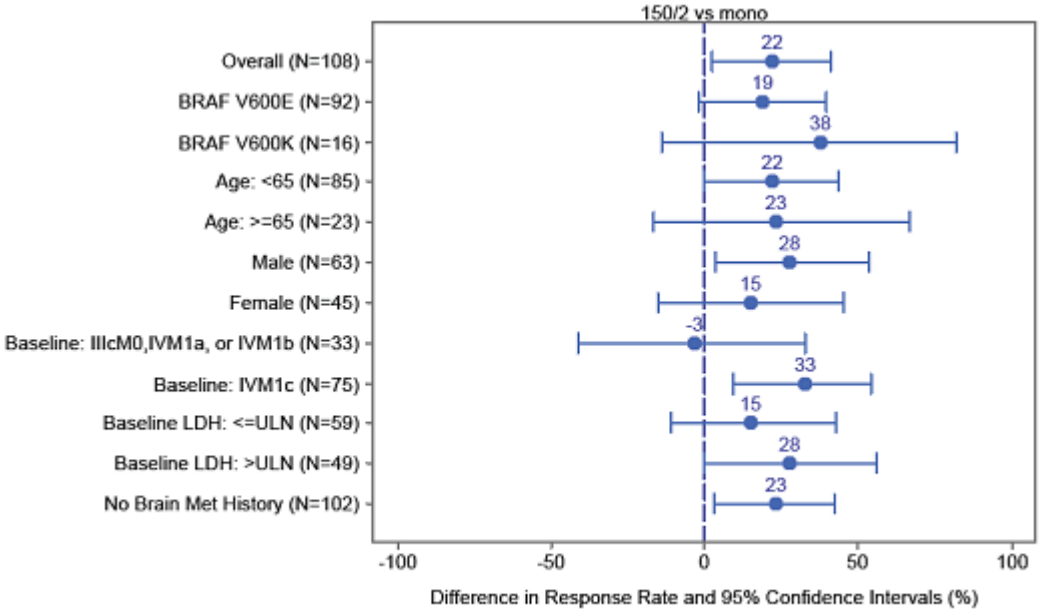
PFS was consistently improved with combination 150/2 therapy relative to dabrafenib monotherapy across all subgroup studied (Figure 23).[25]

Figure 23: Hazard ratios and 95% CI for PFS subgroup analyses in BRF112330 (Part C) (ITT population, May 2012 cut-off) [25]



The differences in ORRs between combination 150/2 therapy and dabrafenib monotherapy generally favoured the combination group in the various subgroups examined (Figure 24), with the exception of subjects with Stage IIIc/IVM0/IVM1a or Stage IVM1b disease at baseline (in which no difference was observed).[114]

Figure 24: Investigator-assessed ORR sub-group analyses in BRF113220 (Part C) (ITT population, May 2012 cut-off) [114]



Conclusion of subgroup analyses

These results indicate that trametinib + dabrafenib combination therapy is more effective than BRAF inhibitor monotherapy regardless of mutation type, gender, age, performance status, baseline LDH and other prognostic factors, and support treatment for all adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, consistent with the licensed indication. We have not considered any subgroup analyses in the economic evaluation.

4.9. Meta-analysis

4.9.1. If a qualitative overview is considered to be appropriate, summarise the overall results of the individual studies with reference to their critical appraisal.

A qualitative discussion/overview of the results of the relevant RCTs is provided in Section 4.13.

A traditional two-stage meta-analysis was not conducted to generate summary statistics for the comparative clinical efficacy of trametinib + dabrafenib combination therapy versus dabrafenib or vemurafenib as monotherapy. As previously explained, the comparative clinical efficacy for trametinib + dabrafenib compared with BRAF inhibitor monotherapy presented in this submission comes directly from the large robust head-to-head Phase III COMBI-d and COMBI-v trials, supported by the Phase II BRF113220 (Part C) study.

For the purposes of the economic evaluation, we have chosen to pool time-to-event data (PFS and OS) from COMBI-d and COMBI-v at the individual patient level. The individual trials were not sufficiently powered to calculate area-under-the curve (AUC) as required in the economic modelling. Pooling data from these trials increases the precision of the estimate of treatment effect for trametinib + dabrafenib combination therapy versus BRAF

inhibitor monotherapy in this respect. It also avoids the need for the underlying but often problematic proportional hazards assumption required in a traditional meta-analysis.

Pooling data from the COMBI-d and COMBI-v studies is justified on the basis of their very high similarity in design, methodology and patient populations. The BRF113220 study was excluded from the pooling because it is a Phase II study with small sample size (approximately 50 patients per treatment arm) and most importantly due to the OS data being heavily confounded by the high rate (83%) of treatment switching from the dabrafenib monotherapy arm to the combination 150/2 arm.

The pooling is discussed in more detail in Appendices 8.13 and summarised as follows: The studies were conducted in similar geographical regions (including Europe, N. America and Australia) in the same time frame such that any differences in supportive care/treatments available is likely to be minimal. The frequency of study visits was the same in both studies as was the nature and timing of all assessments undertaken. Tumour response and progression was assessed according to RECIST v1.1 in both studies.[17; 19] Median follow-up times at the latest data cut-offs are also very similar. Importantly, the eligibility criteria for COMBI-d and COMBI-v were identical (see Table 14) resulting in the populations enrolled in the two studies having highly overlapping baseline demographic and disease characteristics. Indeed, the CHMP has acknowledged their comparable patient populations in the variation assessment report for the use of trametinib in combination with dabrafenib.[37]

The pooling also assumes that the BRAF inhibitors, vemurafenib and dabrafenib, have comparable efficacy; consistent with current clinical opinion, the available clinical evidence and results of indirect comparisons (see Appendix 8.14 for further information). The methodology undertaken for the pooling is further described in Section 5.2.

4.9.2. Methods, limitations, methods, results, assessment of heterogeneity, of a meta-analysis, if performed.

Not applicable. See response to 4.9.1.

4.10. Indirect and mixed treatment comparisons

It has not been necessary to utilise an indirect/mixed treatment comparison in this submission since direct clinical comparisons for the intervention under review, trametinib + dabrafenib combination therapy, versus the comparators dabrafenib and vemurafenib (as monotherapies), are available from the large robust head-to-head Phase III COMBI-d and COMBI-v RCTs, respectively.

COMBI-d evaluated trametinib + dabrafenib versus dabrafenib monotherapy in the relevant patient population - patients with the BRAF V600 mutation-positive unresectable or metastatic melanoma.[17; 18] COMBI-v evaluated trametinib + dabrafenib versus vemurafenib monotherapy in the same patient population.[19; 20] The efficacy and safety results of these studies are presented and discussed fully in Sections 4.7, 4.12, and 4.13.

As discussed above, individual patient level PFS and OS data from these two studies has been pooled for the purposes of the economic evaluation in order to increase the precision of AUC analyses in estimating the treatment effect for trametinib + dabrafenib combination therapy compared with BRAF inhibitor monotherapy.

4.11. Non-randomised and non-controlled evidence

The systemic review was limited to RCTs and therefore no non-RCT evidence was identified by the review. We are not aware of any non-RCT evidence that provides any additional data of value to the decision problem over and above the robust RCT evidence provided by the Phase III COMBI-d and COMBI-v studies, and the randomised Phase II BRF1132220 trial, which is presented and discussed in sections 4.2 to 4.8, 4.12 and 4.13 of this submission.

4.12. Adverse reactions

4.12.1. Evidence from comparative RCTs and regulatory summaries is preferred, but findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse reactions commonly associated with the comparator, or that the occurrence of adverse reactions is not statistically significantly different to those associated with other treatments.

The safety evidence for dabrafenib 150 mg twice daily in combination with trametinib 2mg once daily in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma is derived primarily from the two randomised Phase III studies, COMBI-d (MEK115306) and COMBI-v (MEK116513). This section focusses on the adverse event (AE) data from these two studies, obtained from the latest data cut-offs (12 January 2015 for COMBI-d[18] and 13 March 2015 for COMBI-v[20]) to reflect the longer exposure times. Exceptions include AEs by causality, AEs of special interest and dose modifications for COMBI-v which are taken from the 17 April 2014 data cut[19; 113] based on current availability of data. It should be noted that no new or unexpected safety signals have been identified in these studies with additional follow-up time.

The randomised Phase II study, BRF113220 Part C, provides supportive safety evidence and data are presented for 31 May 2012 and 15 January 2015 cut-offs, depending on data availability. In line with the decision problem, AEs are only presented for the trametinib 2mg o.d. + dabrafenib 150mg b.d. combination arm (150/2) and the dabrafenib monotherapy arm (i.e. not for the trametinib 1mg o.d. + dabrafenib 150mg b.d. [150/1] combination arm).

The methodology, patient disposition, characteristics of participants, endpoints, statistical analysis, critical appraisal and efficacy outcomes for all three studies, are presented in sections 4.1 through to section 4.9 of this submission.

4.12.2. In a table, summarise adverse reactions reported in the studies listed in section 4.2. For each intervention group, give the number with the adverse reaction and the frequency, the number in the group, and the percentage with the reaction. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse reaction.

4.12.2.1 COMBI-d and COMBI-v

4.12.2.1.1 Extent of exposure

Exposure to study treatment in COMBI-d and COMBI-v is presented separately for trametinib, dabrafenib, and vemurafenib (Table 49 and Table 50) and includes treatment beyond progression where applicable. Subjects in the combination arms received close to the targeted daily dose for both trametinib and dabrafenib while on therapy in both studies. The median durations of treatment for the combination arms (11.0 months) were similar in both studies, and longer than for the BRAF inhibitor monotherapy arms. At the time of the

latest data cut-offs, almost half of the subjects in the trametinib + dabrafenib arms in both studies had received more than 12 months of therapy.

Table 49: Summary of exposure to dabrafenib and trametinib in COMBI-d (Safety population, January 2015 cut-off) [18]

	Trametinib or placebo		Dabrafenib	
	Trametinib + dabrafenib N=209	**Dabrafenib + placebo N=211**	**Trametinib + dabrafenib N=209**	**Dabrafenib + placebo N=211**
Daily dose (mg)				
Mean (SD)	1.9 (0.20)	1.9 (0.14)	273.6 (41.44)	284.8 (32.47)
Median (Min, Max)	2.0 (0.9, 2)	2.0 (1.2, 2)	294.7 (125.5,300)	299.6 (118.6, 300)
Time on study treatment (months)				
Mean (SD)	14.4 (9.82)	11.0 (9.10)	14.3 (9.81)	11.1 (9.07)
Median (Min, Max)	11.0 (0, 30)	8.0 (0, 32)	11.0 (0, 30)	8.0 (0, 32)
<3 months, n (%)	16 (8)	34 (16)	16 (8)	33 (16)
3-6 months, n (%)	43 (21)	57 (27)	43 (21)	57 (27)
>6-12 months, n (%)	54 (26)	48 (23)	54 (26)	49 (23)
>12 months, n (%)	96 (46)	72 (34)	96 (46)	72 (34)

Table 50: Summary of exposure to dabrafenib and trametinib in COMBI-v (Safety population, March 2015 cut-off) [20]

	Trametinib + dabrafenib N=350		Vemurafenib N=349
	Trametinib	**Dabrafenib**	
Daily dose (mg)			
Mean (SD)	1.8 (0.28)	261.3 (54.15)	1614.3 (357.14)
Median (Min, Max)	2.0 (0.8, 2)	291.9 (112.4, 300)	1812.9 (450.4, 1920)
Time on study treatment (months)			
Mean (SD)	12.7 (8.73)	12.8 (8.83)	8.5 (7.34)
Median (Min, Max)	11.0 (0, 31)	11.0 (0, 31)	6.0 (0, 29)
<3 months, n (%)	36 (10)	35 (10)	81 (23)
3-6 months, n (%)	84 (24)	84 (24)	96 (28)
>6-12 months, n (%)	70 (20)	70 (20)	88 (25)
>12 months, n (%)	160 (46)	160 (46)	84 (24)

4.12.2.1.2 Adverse Events (COMBI-d & COMBI-v)

Overview of AEs

Almost all patients in COMBI-d and COMBI-v experienced an on-therapy AE (Table 51). In COMBI-d, AEs leading to treatment discontinuation, dose reductions or dose interruptions were more common in the combination arm than the dabrafenib monotherapy arm (11% vs. 7%), whereas in COMBI-v the proportions were generally similar between the combination arm and the vemurafenib arm (16% vs. 14%).

The incidences of SAEs (approximately 40% of patients) were similar across both arms in both studies. A total of 9 patients receiving combination treatment had fatal SAEs across both studies: none were categorised by the investigator as related to study treatment. One subject receiving dabrafenib monotherapy in COMBI-d had a fatal SAE that was considered by the investigator to be related to study treatment (see table footnote for further detail).

Table 51: Overview of AEs in COMBI-d and COMBI-v (Safety populations)[20; 30; 37]

	COMBI-d (Jan 2015 cut-off)		COMBI-v (March 2015 cut-off)	
	Trametinib + dabrafenib N=209	**Dabrafenib monotherapy N=211**	**Trametinib + dabrafenib N=350**	**Vemurafenib monotherapy N=349**
Median follow-up time, months	**20.0**	**16.0**	**19.0**	**15.0**
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[a], n (%)	**88 (42)**	**78 (37)**	**151 (43)**	**136 (39)**
Fatal SAEs[b]	5 (2)	1 (<1)	4 (1)	4 (1)
Fatal SAEs related to study treatment[c]	0	1 (<1)	0	0

AE: Adverse event; CSR = Central serous retinopathy; LVEF: Left ventricular ejection fraction; RVO = Retinal vein occlusion; SAE: Serious adverse event

a. In addition to the standard definition of SAEs, the protocols mandated that the following were to be recorded as SAEs regardless of whether the patients were hospitalised: events of possible drug-induced liver injury with hyperbilirubinemia; any new primary cancer; clinically significant laboratory abnormalities; LVEF decreases meeting protocol-defined stopping criteria; CSR or RVO; pyrexia accompanied by hypotension, dehydration requiring intravenous fluids, or severe rigors/chills

b. *COMBI-d*: Fatal SAEs in the combination therapy arm included cerebral hemorrhage (2 events), cerebrovascular accident (1 event, which was identified as cerebral hemorrhage at the admission CT scan and on later autopsy), myocardial ischemia (this event has been updated to "unknown"; 1 event), and pneumonia (1 event). One patient in the dabrafenib monotherapy arm had an SAE of bile duct adenocarcinoma that was considered by the investigator to be related to study treatment; this event was corrected to a fatal SAE post data-cut off.

COMBI-v: Fatal SAEs in the combination therapy arm: cerebral hemorrhage (2 patients), brain stem haemorrhage (1 patient) and intracranial haemorrhage (1 patient). In the vemurafenib monotherapy arm: acute coronary syndrome, cerebral ischemia, acute coronary syndrome, and pleural infection (1 patient each).

c. One patient in the dabrafenib monotherapy arm in COMBI-d had an SAE of bile duct adenocarcinoma that was considered by the investigator to be related to study treatment; this event was corrected to a fatal SAE post data-cut off.

d. Reflects the number of patients that discontinued either or both trametinib and dabrafenib.

Most Common AEs (COMBI-d and COMBI-v)

The most common AEs (≥20% frequency) reported with trametinib + dabrafenib combination therapy include: pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting and cough (Table 52). The incidences of certain types of AEs were higher in the trametinib + dabrafenib arms compared with the BRAF inhibitor monotherapy arms. In particular, pyrexia appears to occur more frequently with the combination of trametinib + dabrafenib than with dabrafenib monotherapy but is generally manageable with transient treatment interruption and/or use of anti-pyretic medication (see Section on AEs of Special Interest for further details on the presentation and management of pyrexia).

However, the incidences of several dermatological AEs (hyperkeratoses, hand-foot syndrome, alopecia, skin papilloma), particularly those events related to paradoxical activation of the MAPK pathway, were reduced with trametinib + dabrafenib combination therapy compared with BRAF inhibitor monotherapy. Additionally, photosensitivity reactions and sunburn were reported less frequently with trametinib + dabrafenib than with vemurafenib therapy. Arthralgia was also observed less often with trametinib + dabrafenib combination therapy than with vemurafenib alone.[17; 18; 19; 20]

Table 52: AEs occurring in ≥15% of patients in any of the treatment arms in COMBI-d and COMBI-v (Safety populations)

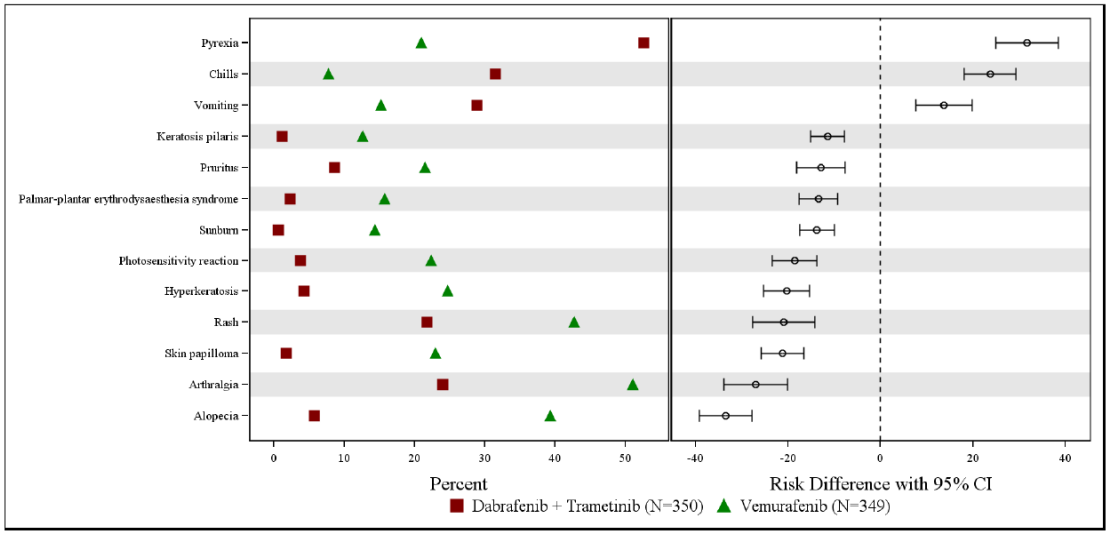
Event, n (%)	COMBI-d (Jan 2015 cut-off)[37]		COMBI-v (March 2015 cut-off)[20]	
	Trametinib + dabrafenib N=209	Dabrafenib monotherapy N=211	Trametinib + dabrafenib N=350	Vemurafenib monotherapy N=349
Median follow-up time, months	**20.0**	**16.0**	**19.0**	**15.0**
Any AE	**203 (97)**	**205 (97)**	**345 (99)**	**345 (99)**
Pyrexia*	119 (57)	69 (33)	193 (55)	74 (21)
Fatigue	81 (39)	79 (37)	110 (31)	117 (34)
Nausea	72 (34)	56 (27)	126 (36)	130 (37)
Headache	69 (33)	63 (30)	112 (32)	84 (24)
Chills	64 (31)	35 (17)	116 (33)	28 (8)
Diarrhoea	63 (30)	33 (16)	120 (34)	136 (39)
Rash	56 (27)	46 (22)	84 (24)	150 (43)
Arthralgia	54 (26)	66 (31)	93 (27)	182 (52)
Hypertension	52 (25)	33 (16)	103 (29)	82 (23)
Vomiting	52 (25)	30 (14)	107 (31)	55 (16)
Cough	44 (21)	44 (21)	77 (22)	40 (11)
Oedema peripheral	44 (21)	19 (9)	48 (14)	42 (12)
ALT increased	28 (13)	12 (6)	49 (14)	61 (17)
Constipation	27 (13)	22 (10)	54 (15)	25 (7)
Myalgia	27 (13)	28 (13)	66 (19)	56 (16)
Asthenia	26 (12)	30 (14)	61 (17)	56 (17)
Back pain	26 (12)	34 (16)	34 (10)	25 (7)
Decreased appetite	26 (12)	28 (13)	44 (13)	70 (20)
Dry skin	26 (12)	34 (16)	33 (9)	67 (19)
Nasopharyngitis	26 (12)	21 (10)	52 (15)	32 (9)
Pruritus	25 (12)	29 (14)	36 (10)	78 (22)

Hyperkeratosis	15 (7)	74 (35)	18 (5)	89 (26)
Hand-foot syndrome†	11 (5)	39 (18)	16 (4)	95 (27)
Alopecia	18 (9)	59 (28)	23 (7)	136 (39)
Skin papilloma	4 (2)	46 (22)	8 (2)	82 (23)
Photosensitivity reaction	5 (2)	6 (3)	15 (4)	81 (23)
Pain in extremity	32 (15)	36 (17)	45 (13)	44 (13)
Sunburn	2 (<1)	1 (<1)	3 (1)	51 (15)

Note: Table does not clinical laboratory evaluations. * Management of pyrexia implemented at ≥38.5°C.
† Includes palmar-plantar erythrodysaesthesia and palmoplantar keratoderma. ALT = Alanine aminotransferase.

Figure 25 presents an analysis of selected AEs for COMBI-v (April 2014 cut-off) based on AEs with a ≥10% difference in incidence between the treatment arms sorted by risk difference. This indicates a higher risk of experiencing pyrexia, chills, and vomiting with trametinib + dabrafenib combination therapy than with vemurafenib monotherapy (i.e. 95% CI excludes 1), whereas the risk of experiencing skin-related toxicities, photosensitivity reaction, sunburn, alopecia and arthralgia is higher with vemurafenib.[113]

Figure 25: Most frequent AEs sorted by Risk Difference in COMBI-v (Safety Population, April 2014 cut-off) [113]



Note: Adverse events were selected based on those with a ≥10% difference in incidence between the treatment arms. Risk Difference >0 indicates a higher risk of experiencing an event in the combination therapy arm than in the vemurafenib monotherapy arm. Risk Difference <0 indicates a higher risk of experiencing an event in the vemurafenib monotherapy arm than in the combination therapy arm. Per the study protocol, adverse events were recorded from the time the first dose of study treatment was administered until 30 days after discontinuation of study treatment.

AEs by maximum grade (COMBI-d & COMBI-v)

Approximately half of the AEs experienced by patients receiving trametinib + dabrafenib combination treatment were mild-to-moderate in severity (Grades 1 and Grade 2). In both Phase III studies, the rates of Grade 3/4 events were higher in the monotherapy arms than in the combination arms (50% vs. 45% in COMBI-d; 57% vs. 66% in COMBI-v). Pyrexia and hypertension were the most common Grade 3/4 events occurring with trametinib + dabrafenib combination therapy in both studies.[37; 156]

Table 53: Grade 3+4 AEs occurring in ≥3% of patients in any of the treatment arms in COMBI-d and COMBI-v (Safety populations)

	COMBI-d (Jan 2015 cut-off)[37]				COMBI-v (March 2015 cut-off) [156]			
	Trametinib + dabrafenib N=209		Dabrafenib monotherapy N=211		Trametinib + dabrafenib N=350		Vemurafenib monotherapy N=349	
Median follow-up time, months	**20.0**		**16.0**		**19.0**		**15.0**	
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)

Note: Table does not clinical laboratory evaluations. AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; SCC = Squamous cell carcinoma; GGT = Gamma glutamyl transferase; NR = Not reported.

AEs by causality (COMBI-d & COMBI-v)

The relative frequencies of AEs considered related to study treatment (Table 54) were similar to the most common AEs overall (Table 52). Again, the incidences of pyrexia and chills were higher in the combination arms in both COMBI-d and COMBI-v studies, while the incidences of hyperkeratoses, alopecia, hand-foot syndrome, skin papilloma were all higher in the BRAF inhibitor monotherapy arms.[18; 37]

Table 54: AEs related to study treatment occurring in ≥15% of patients in any treatment arm in COMBI-d and COMBI-v (Safety populations)

	COMBI-d (Jan 2015 cut-off)[18]		COMBI-v (April 2014 cut-off)[37]	
	Trametinib + dabrafenib N=209	**Dabrafenib monotherapy N=211**	**Trametinib + dabrafenib N=350**	**Vemurafenib monotherapy N=349**
Median follow-up time, months	**20.0**	**16.0**	**11.0**	**10.0**
Any AE related to study treatment, n (%)	**181 (87)**	**189 (90)**	**320 (91)**	**342 (98)**
Pyrexia	108 (52)	52 (25)	163 (47)	54 (15)
Chills	58 (28)	29 (14)	96 (28)	21 (6)
Fatigue	56 (27)	59 (28)	70 (20)	92 (26)
Rash	50 (24)	42 (20)	68 (19)	146 (42)
Nausea	41 (20)	31 (15)	81 (23)	97 (28)
Headache	39 (19)	35 (17)	51 (15)	39 (11)
Diarrhoea	38 (18)	19 (9)	71 (20)	104 (30)
Arthralgia	34 (16)	49 (23)	58 (17)	162 (46)
Vomiting	30 (14)	20 (9)	59 (17)	30 (9)
ALT increased	20 (10)	7 (3)	35 (10)	49 (14)
Dry skin	19 (9)	29 (14)	21 (6)	59 (17)
Pruritus	15 (7)	23 (11)	22 (6)	67 (19)
Hyperkeratosis	13 (6)	70 (33)	12 (3)	79 (23)
Hand-foot syndrome†	13 (6)	57 (27)	14 (4)	94 (27)
Alopecia	10 (5)	55 (26)	18 (5)	136 (39)
Skin papilloma	3 (1)	39 (18)	6 (2)	76 (22)
Myalgia	18 (9)	17 (8)	46 (13)	46 (13)
Decreased appetite	16 (8)	14 (7)	23 (7)	55 (16)
Photosensitivity reaction	3 (1)	5 (2)	12 (3)	78 (22)

Note: Table does not clinical laboratory evaluations. †Includes palmar-plantar erythrodysaesthesia and palmoplantar keratoderma. ALT = Alanine aminotransferase.

Serious Adverse Events (SAEs) (COMBI-d and COMBI-v)

The most frequent SAE in the combination treatment arms of both the COMBI-d and COMBI-v studies was pyrexia, followed by chills and decreased ejection fraction. In the monotherapy treatment arms, pyrexia was the most common SAE observed with dabrafenib, while squamous cell carcinoma was the most common SAE for vemurafenib (Table 55).[20; 37]

Table 55: SAEs occurring in >1% patients in any treatment arm in COMBI-d and COMBI-v (Safety populations)

	COMBI-d (Jan 2015 cut-off)[37]		COMBI-v (March 2015 cut-off)[20]	
	Trametinib + dabrafenib N=209	**Dabrafenib monotherapy N=211**	**Trametinib + dabrafenib N=350**	**Vemurafenib monotherapy N=349**
Median follow-up time, months	**20.0**	**16.0**	**19.0**	**15.0**
Any SAE, n (%)	**88 (42)**	**78 (37)**	**151 (43)**	**136 (39)**
Pyrexia	35 (17)	15 (7)	53 (15)	7 (2)
Chills	9 (4)	3 (1)	14 (4)	0
Ejection fraction decreased	9 (4)	5 (2)	28 (8)	1 (<1)
Basal cell carcinoma	7 (3)	13 (6)	8 (2)	3 (<1)
Hypotension	6 (3)	2 (<1)	5 (1)	0
Pneumonia	6 (3)	2 (<1)	1 (<1)	5 (1)
ALT increased	3 (1)	0	6 (2)	9 (3)
CuSCC/SCC	5 (2)	20 (9)	5 (1)	52 (15)
Dehydration	1 (<1)	2 (<1)	8 (2)	2 (<1)
Hepatic enzyme increased	1 (<1)	0	4 (1)	6 (2)
Blood bilirubin increased	NR	NR	2 (<1)	6 (2)
Urinary tract infection	1 (<1)	1	7 (2)	1 (<1)
Vomiting	3 (1)	0	7 (2)	1 (<1)
Malignant melanoma	1 (<1)	2 (<1)	1 (<1)	6 (2)

Note: Table does not clinical laboratory evaluations. ALT = Alanine aminotransferase; (Cu)SCC = (cutaneous) squamous cell carcinoma; NR = Not reported.

AEs of Special Interest (AESI) (COMBI-d and COMBI-v)

AESIs comprised events that are either known class effects, were identified pre-clinically or in prior clinical studies, or considered potentially life-threatening. Key AESIs included those which were considered most clinically significant based on their implications for patient management or potential for a serious outcome, as well as those with a higher rate of occurrence (Table 56). Consistent with the expected pharmacology, preclinical toxicology profile and mechanism of action of the drugs, and the population treated, AESIs related to dabrafenib are: pyrexia, cutaneous SCCs, other treatment-emergent malignancies including new malignant melanoma, uveitis (incorporated under 'ocular events'), hand-foot syndrome/palmar-plantar erythrodysaesthesia (PPE; incorporated under 'skin-related' toxicities), renal failure and pancreatitis; AESIs related to trametinib are: rash and other skin-related toxicities, diarrhoea, ocular events (including chorioretinopathy/central serous retinopathy), cardiac-related events including left ventricular dysfunction, hypertension, hepatic events, pneumonitis, and oedema. The characteristics of some of the individual AESIs are discussed in more detail below (based on cut-offs dates of January 2015 for COMBI-d and April 2014 for COMBI-v).[37]

Table 56: AEs of Special Interest in COMBI-d and COMBI-v (Safety populations) [37]

	COMBI-d (Jan 2015 cut-off)		COMBI-v (April 2014 cut-off)	
	Trametinib + dabrafenib N=209	**Dabrafenib monotherapy N=211**	**Trametinib + dabrafenib N=350**	**Vemurafenib monotherapy N=349**
Median follow-up time, months	**20.0**	**16.0**	**11.0**	**10.0**
Key events of interest, n (%)				
Pyrexia[a]	129 (62)	79 (37)	200 (57)	89 (26)
Skin-related toxicities	101 (48)	112 (53)	154 (45)	267 (77)
Diarrhoea	63 (30)	33 (16)	112 (32)	131 (38)
Hypertension	54 (26)	36 (17)	94 (27)	90 (26)
Bleeding events	40 (19)	32 (15)	62 (18)	25 (7)
Hepatic events	39 (19)	25 (12)	92 (26)	110 (32)
Ocular events	27 (13)	23 (11)	39 (11)	47 (13)
Cardiac-related events	12 (6)	10 (5)	29 (8)	1 (<1)
Pneumonitis	2 (<1)	0	4 (1)	1 (<1)
Treatment emergent malignancies				
CuSCC[b]	6 (3)	22 (10)	5 (1)	63 (18)
New primary melanoma	1 (<1)	4 (2)	2 (<1)	7 (2)
Other treatment emergent malignancies	3 (1)	7 (3)[c]	3 (<1)	2 (<1)[d]
Other events of interest				
Oedema	53 (25)	23 (11)	68 (18)	44 (13)
Hypersensitivity	35 (17)	14 (7)	36 (10)	44 (13)
Neutropenia	30 (14)	9 (4)	50 (14)	10 (3)
Hyperglycaemia	15 (7)	7 (3)	23 (7)	17 (5)
Renal insufficiency	8 (4)	5 (2)	24 (7)	42 (12)
DVT and PE	6 (3)	2 (<1)	8 (2)	2 (<1)
Pancreatitis	1 (<1)	1 (<1)	2 (<1)	3 (<1)

Note: Table does not clinical laboratory evaluations.

a. Includes pyrexia, influenza-like illness, body temperature increased, sweating, hyperthermia

b. CuSCC = cutaneous squamous cell carcnima: Includes squamous cell carcinoma of the skin, cutaneous, squamous cell carcinoma, keratoacanthoma, Bowen's disease

c. Includes 1 subject who was mistakenly reported as having cutaneous events of cuSCC and basal cell carcinoma as well as non-cutaneous treatment-emergent malignancies

d. Includes 1 subject who upon subsequent clinical review was identified as having carcinoma in situ of skin.

DVT = Deep vein thrombosis; PE = Pulmonary embolism

Pyrexia

Overall, pyrexia was reported at a higher rate with trametinib + dabrafenib combination therapy than with either dabrafenib or vemurafenib monotherapy. Most pyrexia events associated with combination therapy were Grades 1 or 2; ≤7% of patients overall had Grade 3 pyrexia events. However, a higher percentage of patients on combination therapy had Grade 3 pyrexia than those on dabrafenib or vemurafenib monotherapy. No Grade 4 pyrexia events were reported in either study (Table 53) but 11-14% of patients on the combination were hospitalised due to pyrexia compared to 5% for dabrafenib monotherapy and 1% for vemurafenib (Table 57).[37]

Pyrexia events in the combination arms generally occurred early in the course of treatment (median time to onset 29-38 days), with approximately a half reported within the first month

of therapy. The median duration of the initial pyrexia event for patients on combination therapy was 3 days (Table 57). Of those patients who experienced pyrexia, at least one half had no more than 1 or 2 episodes.[17; 21; 37]

The SPC for dabrafenib advises initiation of anti-pyretic medication (paracetamol or nonsteroidal anti-inflammatory drugs [NSAIDS]) and/or interruption of dabrafenib treatment if a patient's body temperature ≥38.5^{o}C. Dabrafenib may be re-started at the same dose once the patient has been afebrile for 24 hours or at a reduced dose if deemed clinically appropriate (trametinib may be continued at the same dose). Short-courses of low-dose oral corticosteroids may be required in recurrent or more severe cases.[19; 21]

Our economic model assumes that the management of a Grade 3 pyrexia event involves an in-patient stay (weighted average of a 4 to 5 day stay) and a consultant-led follow-up visit. In clinical practice, a patient will more likely be managed less intensively with a full blood count (to eliminate neutropenia), a brief period of observation before being allowed home, treatment interruption (typically lasting 3 days), and a follow-up visit with a nurse prior to re-initiation of treatment.

Table 57: Characteristics of pyrexia and pyrexia-related events in COMBI-d and COMBI-v (Safety populations)

	COMBI-d (January 2015 cut-off[111]				COMBI-v (April 2014 cut-off[113]		
	Trametinib + dabrafenib (N=209)		Dabrafenib monotherapy (N=211)		Trametinib + dabrafenib (N=350)		Vemurafenib monotherapy (N=349)
Median follow-up time, months	20.0		16.0		11.0		10.0
No. (%) of subjects with event	129 (62)		79 (37)		200 (57)		89 (26)
No. of events	498		145		555		131
Event type							
Pyrexia	119 (57)		69 (33)		184 (53)		73 (21)
Influenza-like illness	17 (8)		11 (5)		30 (9)		14 (4)
Body temperature increased	4 (2)		3 (1)		9 (3)		7 (2)
Sweating	4 (2)		0		0		0
Hyperthermia	2 (<1)		1 (<1)		4 (1)		1 (<1)
No. of occurrences, n (%)							
One	41/209 (20)		46/211 (22)		83/350 (24)		65/349 (19)
Two	19/209 (9)		18/211 (9)		40/350 (11)		16 (349 (5)
Three or more	69/209 (33)		15/211 (7)		77/350 (22)		8/349 (2)
Outcome, n (%)[b]							
Recovered/resolved	115/209 (55)		73/211 (35)		189/350 (54)		85/349 (24)
Recovering/resolving	1/209 (<1)		0		4/350 (1)		2/349 (<1)
Not recovering	7/209 (3)		3/211 (1)		6/350 (2)		2/349 (<1)
Recovered with sequelae	6/209 (3)		3/211 (1)		1/350 (<1)[f]		0
Fatal	0		0		0		0
Maximum Grade, n (%)							
Grade 1	58/209 (28)		47/211 (22)		94/350 (27)		62/349 (18)
Grade 2	55/209 (26)		28/211 913)		84/350 (24)		24/349 (7)
Grade 3	16/209 (8)		4/211 (2)		21/350 (6)		2/349 (<1)
Grade 4	0		0		0		0
Actions taken, n (%)[c]	**Dabrafenib**	**Trametinib**	**Dabrafenib**	**Placebo**	**Dabrafenib**	**Trametinib**	**Vemurafenib**
Permanently discontinued	5/209 (2)[d]	4/209 (2)[d]	2/211 (<1)[e]	1/211 (<1)[e]	13/350 (4)	3/350 (<1)	1/349 (<1)
Dose reduced	29/209 (14)	6/209 (3)	6/211 (3)	2/211 (<1)	50/350 (14)	10/350 (3)	10/349 (3)
Dose not changed	96/209 (46)	116/209 (56)	59/211 (28)	73/211 (35)	135/350 (39)	181/350 (52)	77/349 (22)
Dose interrupted/delayed	74/209 (35)	40/209 (19)	29/211 (14)	13/211 (6)	109/350 (31)	47/350 (13)	16/349 (5)
Management, n (%)							
Paracetamol /anti-pyretic[g]	72 (34)		32 (15)		103 (29)		23 (7)
Ibuprofen / NSAID[g]	20 (10)		8 (4)		46 (13)		10 (3)
Prednisolone / Corticosteroid[g]	10 (5)		2 (<1)		29 (8)		1 (<1)

Hospitalisation	29/204 (14)	11 (5)	39 (11)	5 (1)
Time to onset of first occurrence (weeks)				
Median (Min-Max)	38 (1-716)	20 (1-698)	29 (1-399)	13 (1-428)
Duration of occurrence (days)				
Median (Min-Max)	3 (1-53)	3 (1-57)	3 (1-53)	4 (1-76)

a. Subjects may be included in more than one category for “Event Characteristics.” b. Outcome worst case hierarchy: Fatal > Not Recovered/Not Resolved > Recovering/Resolving with sequelae >Recovering/Resolving > Recovered/Resolved. c. Subjects are counted once under each action that was taken. d. Both dabrafenib and trametinib in 5 subjects.
e. Both dabrafenib and placebo in 2 subjects. f. Sequelae were recorded as fever. g. Medications for active management of pyrexia.

Treatment-emergent malignancies

(i) Cutaneous Squamous Cell Carcinoma (CuSCC)

CuSCCs have been reported as a class effect of BRAF inhibitors and are consistent with the mechanism of paradoxical MAPK-activation in cells with pre-existing RAS mutations.[24; 157] CuSCC events (including squamous cell carcinoma of the skin, keratoacanthoma and Bowen's disease) occurred at low frequencies (1%-3% of patients) in the combination arms of both Phase III studies, and were less frequent compared to either the dabrafenib (10%) or vemurafenib (18%) monotherapy arms. There were no Grade 4 cuSCCs events in the combination arms in either study. The majority of events did not lead to dose modification or withdrawal in any treatment arm. The median time to onset of the first occurrence of cuSCC was longer on combination therapy (139-223 days) compared to BRAF inhibitor monotherapy (60-63 days). The majority of patients with cuSCC in had one or two occurrences that recovered following excision.[18; 19; 37]

(ii) New primary melanoma

Across both Phase III studies, new primary melanoma occurred at a low frequency (≤1%) in the combination arms and at 2% in both BRAF inhibitor monotherapy arms. The majority of events in all treatment arms did not lead to dose modification or withdrawal of study drug. The median time to onset of the first occurrence of a new primary melanoma event was longer for patients in both combination arms compared to the monotherapy arms (approximately 245 versus 60 days).[18; 19; 37]

(iii) Other treatment-emergent malignancies

The overall incidence of other treatment-emergent malignancies was low in the combination arms (≤1%) in both Phase III studies with a median time to onset of 239-330 days. Most events did not lead to dose modification and only one patient on combination treatment discontinued due to the event.[37]

Other skin-related toxicities

The percentage of patients with skin-related toxicities (other than cutaneous secondary malignancies) was similar across the combination arms (45-48%) and dabrafenib monotherapy arm (53%), and higher in the vemurafenib monotherapy arm (77%). Approximately half of all skin-related toxicities reported in the COMBI-d and COMBI-v studies were events of rash. While the rates of rash did not differ greatly between combination therapy and dabrafenib monotherapy in COMBI-d (27% vs. 22%), rash was almost twice as frequent with vemurafenib monotherapy as with combination treatment in COMBI-v (43% vs. 22%).[19; 37] Hyperkeratosis and hand-foot syndrome/palmar-plantar erythrodysaesthesia (PPE) were also far more prevalent with BRAF inhibitor monotherapy than with combination therapy. Dermatitis acneiform, a toxicity associated with trametinib[41] was seen more frequently with the combination than with dabrafenib monotherapy (10% vs. 4%) in COMBI-d, but occurred at the same rates (6%) in the combination and vemurafenib arms in COMBI-v.[19; 111; 113; 37] Interestingly, dermatitis acneiform appears to be reduced when dabrafenib and trametinib are co-administered compared to the use of trametinib in monotherapy.[25; 41]

The great majority of skin-related AEs in the two studies were Grades 1 or 2; ≤2% of patients receiving combination treatment and dabrafenib monotherapy had a Grade 3 skin-related event compared with 16% of patients on vemurafenib monotherapy (primarily related to rash). No Grade 4 skin-related toxicities were reported in either study. Most patients did not require a dose modification in relation to a skin-related AE and approximately two-thirds had events that resolved. Median time to onset of the first occurrence of a skin-related toxicity was longer in patients receiving combination therapy (36-40 days versus 10-17 days on BRAF inhibitor monotherapy), with a medium duration of around 30 days.[111; 113]

Hypertension

Hypertension was more common in the combination arms and the vemurafenib monotherapy arm across both Phase III studies (26-27%), and was lower in the dabrafenib monotherapy arm (17%). Grade 3 events occurred in 6-14% of patients receiving combination treatment versus 6-9% on BRAF inhibitor monotherapy. Baseline hypertension was high in a number of patients who experienced Grade 3 hypertension. No Grade 4 events were reported for combination therapy. Median time to onset of first occurrence was 56-58 days for the combination, with a median duration of 27-29 days. Of patients with hypertension events, most did not require dose modification and no treatment discontinuations were required.[37] Regular blood pressure monitoring is recommended during trametinib + dabrafenib treatment.[22]

Bleeding events

Bleeding events occurred with the following incidences in the Phase III studies: combination arms (18-19%), dabrafenib monotherapy (15%) and vemurafenib (7%). The most common bleeding event in the combination arms in both studies was epistaxis. Gastrointestinal, genitourinary, pulmonary, and intracranial bleeding were also reported. The majority of bleeding events were Grade 1 and not serious, not considered to be related to study treatment by the investigator, and resolved without dose modification. Grade 3 events occurred with a frequency of <1% in any treatment arm. Across the studies, 6 subjects in the combination arms and no subjects in the BRAF inhibitor monotherapy arms had fatal intracranial haemorrhages; none were considered related to study treatment by the investigator. Confounding factors were present in 5 of the 6 fatal cases (e.g. use of anticoagulant therapy, presence of brain metastases, and cerebral haemorrhage after a fall in the setting of thrombocytopenia). Median time to onset of first bleeding event was approximately 3 months for the combination.[37]

Cardiac-related events

Cardiac-related events comprised decreased ejection fraction or left ventricular dysfunction/cardiac failure and occurred with the following incidences: combination therapy and dabrafenib monotherapy (5-8%) and vemurafenib arm (<1%). Most cardiac-related events were Grades 2 or 3, serious, led to dose interruption (as mandated by the study protocols). No Grade 4 cardiac-related events were reported. Median time to first occurrence of cardiac-related events was 88-157 days for the combination, with a median duration of 24-27 days.[37]

One or both study treatments were withdrawn due to cardiac-related events for ≤3% of patients in the combination arm.[37] The majority of the LVEF decreases that met interruption criteria in the combination arms of the studies were reported as asymptomatic and resolved. Seventeen patients in the combination arms of the two studies were re-challenged; only four of the 17 met LVEF dose interruption criteria following re-challenge. These findings suggest that by detecting LVEF decreases early through regular monitoring and by interrupting trametinib at the time of first occurrence, more severe sequelae may be prevented.[111; 113] The trametinib SPC provides recommendations regarding evaluation and management of LVEF in patients receiving trametinib + dabrafenib combination therapy and guidance for re-initiation of treatment once an episode resolves.[22]

Ocular events

The percentage of patients experiencing ocular events was similar across the treatment arms of the Phase III studies (11-13%). Most patients who experienced an ocular event had a single event that was considered related to study treatment.[37] In COMBI-d, three patients on combination therapy and none on dabrafenib monotherapy had Grade 3 ocular events (uveitis, iridocyclitis, retinal detachment). In COMBI-v, there were two Grade 3 ocular events reported in the combination arm (uveitis, iridocyclitis) and four cases in the vemurafenib arm (reduced visual acuity, retinal degeneration, and 2 uveitis events). There were no Grade 4 ocular events in any treatment arm in either study. No cases of RVO were reported in either study. Most patients with ocular events did not require dose modification and discontinuation of study treatment was reported for <1% of patients.[111; 113] Patients should be monitored for visual problems (changes in vision, blurred vision, photophobia, eye pain) while on trametinib + dabrafenib combination therapy and referred to an ophthalmologist if required.[21; 22]

Hepatic disorders

The most frequent hepatic events reported in both treatment arms in both studies were increased ALT and increased AST. GGT was not routinely collected in the COMBI-d study, most likely contributing to the higher incidence of hepatic events noted in the COMBI-v. Grade 3 hepatic events were reported in 7-9% of patients receiving combination therapy (the most frequent Grade 3 events were increased AST / ALT / GGT) versus 1% of patients on dabrafenib monotherapy and 10% of patients on vemurafenib; the corresponding figures for grade 4 events were <1%, <1% and 2%. Combination treatment was discontinued due to a hepatic event in up to 2% of patients, and dose reductions were noted in up to 4% of patients. At least two-thirds of hepatic events associated with combination therapy in the Phase III studies resolved.[37] Regular liver function monitoring is recommended in patients receiving trametinib + dabrafenib combination therapy.[21; 22]

Renal insufficiency

Renal insufficiency was reported in 4-7% of patients on combination treatment (Grade 3 in ≤1%; Grade 4 in one patient; median time to first occurrence 108-147 days with median duration of 4-16 days) compared with 2% of patients on dabrafenib monotherapy which was lower than noted for vemurafenib (12%).[37] Renal failure was observed in ≤1 % of patients receiving the combination.[21] Four patients on combination therapy discontinued treatment

due to the event.[37] Routine monitoring of serum creatinine is advised in patients receiving trametinib + dabrafenib combination therapy, with interruption of dabrafenib as clinically appropriate if creatinine increases.[21]

Oedema events

Oedema was more common with combination treatment (18-25%; Grade 3 ≤1%; median time to first occurrence 113-130 days with median duration of 29-37 days) than with dabrafenib monotherapy (11%) or vemurafenib (13%). In both studies, Grade 3 oedema events were reported in <1% of patients in both treatment arms, and there were no Grade 4 events or oedema SAEs in either arm. Discontinuation due to an oedema event and dose reduction were reported in <1% of patients on combination treatment.[37]

QT prolongation

For combination therapy, an AE of QTc prolongation was reported in no patient in the COMBI-d study and in 5 patients in the COMBI-v study; 4 patients had an increase to >500 msec, including 2 patients who also had an increase >60 msec from baseline that subsequently resolved.[37; 21] QTc prolongation was reported for 5 patients on dabrafenib monotherapy and 12 patients on vemurafenib.[37] The dabrafenib SPC provides recommendations on the monitoring for, and management of, QT prolongation.[21]

Neutropenia

Neutropenia was more common with combination treatment (14%; Grade 3 in 4-7%; Grade 4 in <1%) than with dabrafenib (4%) or vemurafenib (3%) monotherapies. Treatment discontinuation due to the event was reported for one patient on combination therapy, with dose reductions required for up to 3% of patients and dose interruptions for up to 7%.[37]

Pancreatitis

Pancreatitis was reported for 3 patients (<1%) on combination treatment with one Grade 4 event; no dose adjustments were required.[37]

Pulmonary embolism (PE) and Deep vein thrombosis (DVT)

PE and DVT were reported in 2-3% of patients on combination treatment (Grade 3 in 1-2%; Grade 4 in one patient), higher than noted for the monotherapy arms (<1%). While dose interruption due to the event was reported for 3 patients on combination treatment, no patient had their dose reduced or discontinued study treatment.[37]

4.12.2.1.3 Dose modifications due to AEs (COMBI-d and COMBI-v)

<u>AEs leading to permanent treatment discontinuation (COMBI-d and COMBI-v)</u>

The incidence of AEs leading to permanent discontinuation of study treatment was higher in the combination arm than in the dabrafenib monotherapy arm in the COMBI-d study, but was similar between the two treatment arms in the COMBI-v study. The most common AEs

leading to permanent discontinuation of trametinib + dabrafenib therapy was pyrexia (≤4%) and decreased ejection fraction (≤3%) (Table 58).

Table 58: AEs leading to permanent discontinuation of study treatment in ≥1% of patients in any treatment arm in COMBI-d and COMBI-v (Safety Populations)

	COMBI-d (Jan 2015 cut-off)[30]		COMBI-v (March 2015 cut-off)[20]	
	Trametinib + dabrafenib N=209	**Dabrafenib monotherapy N=211**	**Trametinib + dabrafenib N=350**	**Vemurafenib monotherapy N=349**
Median follow-up time, months	**20.0**	**16.0**	**19.0**	**15.0**
Any Event, n (%)	**24 (11)**	**14 (7)**	**55 (16)**	**48 (14)**
Pyrexia	5 (2)	2 (<1)	14 (4)	1 (<1)
Ejection fraction decreased	3 (1)	3 (1)	12 (3)	0
ALT increased	2 (<1)	0	5 (1)	4 (1)
Arthralgia	1 (<1)	0	1 (<1)	6 (2)
AST increased	1 (<1)	0	3 (<1)	5 (1)

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase

AEs leading to dose interruptions or dose reductions (COMBI-d and COMBI-v)

Across the COMBI-d and COMBI-v studies, the percentage of patients requiring dose interruptions due to AEs were similar in both combination arms and in the vemurafenib arm, and occurred to a lesser extent in the dabrafenib monotherapy arm (Table 59).

Dose reductions due to AEs were higher in the combination arm than the dabrafenib arm in COMBI-d, and occurred in 33% and 39% of patients receiving combination therapy and vemurafenib monotherapy, respectively, in COMBI-v (Table 60).

The most common AE leading to dose interruption and dose reduction in the combination arms was pyrexia (note that dose interruption due to pyrexia was part of protocol-specific management in the studies). In the vemurafenib monotherapy arm, the most common AE leading to dose modification was rash.[37]

Table 59: AEs leading to dose interruptions ≥3% of patients in any treatment arm in COMBI-d and COMBI-v (Safety Populations) [37]

	COMBI-d (Jan 2015 cut-off)		COMBI-v (April 2014 cut-off)	
	Trametinib + dabrafenib N=209	**Dabrafenib monotherapy N=211**	**Trametinib + dabrafenib N=350**	**Vemurafenib monotherapy N=349**
Median follow-up time, months	**20.0**	**16.0**	**11.0**	**10.0**
Any Event, n (%)	**118 (56)**	**78 (37)**	**192 (55)**	**197 (56)**
Pyrexia	73 (35)	29 (14)	106 (30)	14 (4)
Chills	22 (11)	8 (4)	27 (8)	2 (<1)
Vomiting	15 (7)	3 (1)	15 (4)	6 (2)
Ejection fraction decreased	10 (5)	4 (2)	20 (6)	0
Diarrhoea	9 (4)	2 (<1)	15 (4)	8 (2)

Fatigue	8 (4)	5 (2)	10 (3)	10 (3)
Headache	7 (3)	2 (<1)	8 (2)	1 (<1)
Hypotension	6 (3)	3 (1)	7 (2)	1 (<1)
ALT increased	5 (2)	2 (<1)	13 (4)	21 (6)
AST increased	4 (2)	2 (<1)	7 (2)	14 (4)
Arthralgia	3 (1)	0	6 (2)	22 (6)
Neutropenia	3 (1)	1 (<1)	20 (6)	3 (<1)
Rash	2 (<1)	3 (1)	9 (3)	48 (14)
Rash maculopapular	0	2 (<1)	3 (<1)	13 (4)
Blood creatinine increased	1 (<1)	0	3 (<1)	14 (4)
Dehydration	1 (<1)	3 (1)	9 (3)	1 (<1)
GGT increased	0	2 (<1)	10 (3)	7 (2)

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = gamma glutamyl transferase.

Table 60: AEs leading to dose reductions in ≥3% of patients in any treatment arm in COMBI-d and COMBI-v (Safety Populations) [37]

	COMBI-d (Jan 2015 cut-off)		**COMBI-v (April 2014 cut-off)**	
	Trametinib + dabrafenib N=209	**Dabrafenib monotherapy N=211**	**Trametinib + dabrafenib N=350**	**Vemurafenib monotherapy N=349**
Median follow-up time, months	**20.0**	**16.0**	**11.0**	**10.0**
Any Event, n (%)	**59 (28)**	**29 (14)**	**115 (33)**	**136 (39)**
Pyrexia	29 (14)	6 (3)	49 (14)	10 (3)
Ejection fraction decreased	4 (2)	1 (<1)	13 (4)	0
Rash	4 (2)	2 (<1)	5 (1)	37 (11)
Rash maculopapular	0	2 (<1)	2 (<1)	10 (3)
ALT increased	3 (1)	0	2 (<1)	11 (3)
Fatigue	3 (1)	3 (1)	1 (<1)	9 (3)
Arthralgia	1 (<1)	0	4 (1)	17 (5)

ALT = Alanine aminotransferase

4.12.2.1.4 Subgroup analysis of AEs by age

In both the COMBI-d and COMBI-v studies, the percentage of patients with any AE was similar between the age subgroups (<65 years and ≥65 years) and across the treatment arms, and was consistent with the findings within the overall Safety populations. The percentage of patients with Grade 3+ AEs, SAEs, AEs leading to treatment discontinuation or dose modification (reduction or interruption) was higher in those ≥65 years old than in those <65 years old in both treatment arms. [37]

4.12.2.1.5 Laboratory findings

Clinical chemistry assessments

In COMBI-d, a higher percentage of patients in the combination arm than in the dabrafenib monotherapy arm had “any grade” increases in hypoalbuminaemia (53% [with 1% grade 3] vs 27%), hypokalaemia (13% [with 2% grade 3] vs. 10%) and hyponatraemia (24% [with 6% grade 3] vs. 14%). For the combination arm, one grade 4 event was reported (hyperglycaemia).[37]

In COMBI-v, a higher percentage of patients on combination therapy than vemurafenib monotherapy had “any grade” changes from baseline in hypoalbuminaemia (45% [with <1% grade 3] vs. 15%) and hypophosphataemia (39% [with 7% grade 3 and 1 grade 4 event] vs. 23%). A lower percentage of patients had “any grade” change from baseline in creatinine in the combination arm compared with the vemurafenib arm (12% vs. 35%). For the combination arm, six grade 4 events were reported; creatinine increase (n=1), hyperglycaemia (n=3), hyponatraemia (n=1), and hypophosphataemia (n=1).[37]

Haematology assessments

In COMBI-d, the percentage of patients with increases of any grade and to Grade 3 neutropenia from baseline was higher in the combination arm than in the dabrafenib monotherapy arm. The percentage of patients with changes from baseline to Grade 3/4 in haemoglobin increase, and lymphocyte / leucocyte / platelet count decreases, were similar between the treatment arms.[37]

In COMBI-v, the percentage of patients with a change from baseline of any grade and to Grade 3 neutropenia and leucopenia was higher in the combination arm than in the vemurafenib arm. The percentages of patients with changes from baseline to Grade 3 or Grade 4 in haemoglobin increase, and lymphocyte and platelet count decreases were similar between the treatment arms.[37]

4.12.2.2 BRF113220 (Part C)

4.12.2.2.1 Extent of exposure (BRF113220)

The median daily dose of dabrafenib and trametinib in the combination 150/2 group was close to the targeted daily dose (Table 61).

Table 61: Summary of exposure in BRF113220 (All-treated population, May 2012 cut-off)[114]

	Treatment Groups	
	Dabrafenib + trametinib 150/2 N=55[a]	**Dabrafenib monotherapy N=53[a]**
Dabrafenib		
Daily Dose (mg)		
Mean (SD) Median (Min, Max)	253.29 (56.099) 281.75 (121.5, 300.0)	288.36 (20.784) 295.91 (165.6, 300.0)
Time on Study Treatment (months)		
Mean (SD) Median (Min, Max)	9.848 (4.1659) 10.940 (1.87 - 17.28)	6.498 (3.2696) 6.078 (1.81 - 15.21)
Trametinib		
Daily Dose (mg)		
Mean (SD) Median (Min – Max)	1.76 (0.345) 1.92 (0.3 - 2.0)	NA NA
Time on Study Treatment (months)		
Mean (SD) Median (Min – Max)	9.673 (4.1638) 10.908 (1.77 - 17.28)	NA NA

a. One patient randomised to the dabrafenib monotherapy arm received trametinib + dabrafenib combination therapy (150/2) (n=55) due to a dispensing error.

4.12.2.2.2 Adverse events (AEs) (BRF113220)

Overview of AEs (BRF113220)

The overall incidences of AEs leading to dose reduction, interruption, or permanent discontinuation of study drug, SAEs, drug-related SAEs, and fatal SAEs were all higher in the combination 150/2 arm than in the dabrafenib monotherapy arm (Table 62). None of the three fatal SAEs reported in the combination group were considered drug-related by the investigator.

Table 62: Overview of AEs in BRF113220 (All-Treated population) [37; 114]

	31 May 2012 cut-off		15 January 2015 cut-off	
	Trametinib + dabrafenib 150/2 N=55[a]	**Dabrafenib mono therapy N=53[a]**	**Trametinib + dabrafenib 150/2 N=55[a]**	**Dabrafenib mono therapy N=53[a]**
Median follow-up time	**14.1 months**		**~46 months**	
Any AE, n (%)	**55 (100)**	**53 (100)**	**55 (100)**	**53 (100)**
AEs leading to permanent discontinuation of study drug	5 (9)	1 (2)	8 (15)	1 (2)
AEs leading to dose reduction	27 (49)	11 (21)	33 (60)	13 (25)
AEs leading to dose interruption	37 (67)	18 (34)	40 (73)	18 (34)
Any SAE[b], n (%)	**34 (62)**	**13 (25)**	**38 (69)**	**14 (26)**
Drug-related SAEs	23 (42)	10 (19)	25 (45)	10 (19)
Fatal SAEs	3 (5)	0	4 (7)	0
Drug-related fatal SAEs	0	0	0	0

a. One patient randomised to the dabrafenib monotherapy arm received trametinib + dabrafenib combination therapy (150/2) (n=55) due to a dispensing error.
b. In addition to the standard definition of SAEs, the protocol mandated that the following events were to be reported as SAEs, regardless of whether the subjects were hospitalized: cuSCC; LVEF decreases meeting protocol-defined stopping criteria; CSR or RVO, valvular toxicity meeting protocol-defined stopping criteria; new primary cancers; and pyrexia accompanied by hypotension and/or rigors/chills. Therefore, the total incidence of SAEs is higher than the incidence of SAEs that led to hospitalisation.

Most common AEs (BRF113220)

Consistent with the Phase III studies, pyrexia, chills fatigue, nausea, vomiting and diarrhoea were among the most common AEs reported in the combination 150/2 group, and the incidence of these AEs were higher than those in the dabrafenib monotherapy group (Table 63). No new safety signals were observed in the updated analysis (January 2015 cut-off) compared with the previous safety analysis; the incidences of some AEs have stayed very similar (e.g. pyrexia, chills, rash) while the incidences of other AEs have increased slightly with the longer exposure time, but the pattern remains the same.[25; 26]

Table 63: AEs experienced by >20% of patients in either treatment arm in BRF113220 (All-treated population)

	31 May 2012 cut-off [25]		15 January 2015 cut-off [26]	
	Trametinib + dabrafenib 150/2 N=55[a]	**Dabrafenib monotherapy N=53[a]**	**Trametinib + dabrafenib 150/2 N=55[a]**	**Dabrafenib monotherapy N=53[a]**
Median follow-up time	**14.1 months**		**~46 months**	
Any AE, n (%)	**55 (100)**	**53 (100)**	**55 (100)**	**53 (100)**
Pyrexia	39 (71)	14 (26)	38 (69)	14 (26)
Chills	32 (58)	9 (17)	33 (60)	9 (17)
Fatigue	29 (53)	21 (40)	32 (58)	22 (42)
Diarrhoea	20 (36)	15 (28)	27 (49)	15 (28)
Nausea	24 (44)	11 (21)	26 (47)	11 (21)
Vomiting	22 (40)	8 (15)	26 (47)	8 (15)
Arthralgia	15 (27)	18 (34)	19 (35)	17 (32)
Cough	16 (29)	11 (21)	19 (35)	11 (21)
Headache	16 (29)	15 (28)	17 (31)	17 (32)
Rash	16 (29)	19 (36)	17 (31)	19 (36)
Decreased appetite	12 (22)	10 (19)	16 (29)	11 (21)
Constipation	12 (22)	6 (11)	15 (27)	6 (11)
Night sweats	13 (24)	3 (6)	15 (27)	3 (6)
Oedema peripheral	16 (29)	9 (17)	14 (25)	9 (17)
Myalgia	12 (22)	6 (11)	13 (24)	12 (23)
Abdominal pain	9 (16)	4 (8)	12 (22)	7 (13)
Actinic keratosis	8 (15)	5 (9)	12 (22)	7 (13)
Anaemia	7 (13)	3 (6)	12 (22)	4 (8)
Back pain	10 (18)	6 (11)	12 (22)	6 (11)
Dry skin	10 (18)	3 (6)	12 (22)	2 (4)
Pain in extremity	9 (16)	10 (10)	12 (22)	11 (21)

a. One patient randomised to the dabrafenib monotherapy arm received trametinib + dabrafenib combination therapy (150/2) (n=55) due to a dispensing error.

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

AEs by maximum grade (BRF113220)

The proportion of patients experiencing AEs Grade≥3 was higher in the combination 150/2 group compared with the dabrafenib monotherapy group (Table 64). AEs Grade≥3 in the combination group included 3 fatal SAEs, which were not considered drug-related by the study investigator. The incidence of Grade 3 AEs was similar between the treatment arms,

whereas the incidence of Grade 4 AEs was higher in the combination arm. The most common AEs of Grades 3 or 4 were neutropenia and hyponatraemia in the combination group, and SCC/SCC of the skin / keratoacanthoma in the dabrafenib monotherapy group.

Table 64: Summary of Grade 3 or Grade 4 AEs experienced by ≥2 patients in either treatment arm in BRF113220 (All treated population, May 2012 cut-off) [25; 114]

	Treatment arms					
	Dabrafenib + trametinib 150/2 N=55[a]			**Dabrafenib monotherapy N=53[a]**		
Median follow-up time	**14.1 months**			**~46 months**		
Grade	**Any**	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**
Any AE, n (%)	**55 (100)**	**25 (45)**	**7 (13)[c,d]**	**53 (100)**	**22 (42)**	**1 (2)[b]**
Neutropenia	8 (15)	3 (5)	3 (5)	1 (2)	1 (2)	0
Hyponatremia	5 (9)	4 (7)	0	1 (2)	0	0
Back pain	10 (18)	3 (5)	0	6 (11)	1 (2)	0
Lymphopenia	3 (5)	3 (5)	0	1 (2)	0	0
Pulmonary embolism	3 (5)	2 (4)	0	0	0	0
Pyrexia	39 (71)	3 (5)	0	14 (26)	0	0
Renal failure acute	3 (5)	3 (5)	0	0	0	0
ALT increased	5 (9)	2 (4)	0	1 (2)	0	0
Anaemia	7 (13)	2 (4)	0	3 (6)	0	0
Fatigue	29 (53)	2 (4)	0	21 (40)	3 (6)	0
GGT increased	5 (9)	2 (4)	0	1 (2)	0	0
Pneumonia	2 (4)	2 (4)	0	1 (2)	1 (2)	0
SCC	2 (4)	2 (4)	0	4 (8)	4 (8)	0
SCC of skin	1 (2)	1 (2)	0	6 (11)	5 (9)	0
Keratoacanthoma	1 (2)	0	0	6 (11)	2 (4)	0
Syncope	2 (4)	2 (4)	0	0	0	0
Hyperkalemia	1 (2)	1 (2)	0	4 (8)	2 (4)	0
Hypokalemia	5 (9)	0	1 (2)	3 (6)	2 (4)	0
Muscular weakness	3 (5)	1 (2)	0	0	0	0
Nausea	24 (44)	1 (2)	0	11 (21)	0	0
Vomiting	22 (40)	1 (2)	0	8 (15)	0	0
Atrial fibrillation	1 (2)	0	0	2 (4)	2 (4)	0

ALT=Alanine aminotransferase; GGT=Gamma glutamyl transferase; SCC=squamous cell carcinoma.

a. One patient randomised to the dabrafenib monotherapy arm received trametinib + dabrafenib combination therapy (150/2) (n=55) due to a dispensing error.

Note: Due to the cut-off applied for reporting events in the summary table, some Grade 4 events are not included in the table; these events are listed by treatment arm as follows:

(i) One patient in the dabrafenib monotherapy arm experienced Grade 4 spinal compression fracture.

(ii) In addition to Grade 4 neutropenia (3 patients; shown in table) and Grade 4 hypokalemia (1 patient; shown in table), other Grade 4 AEs were gastric haemorrhage (1 patient), thrombocytopenia (1 patient), increased blood creatinine (1 patient), and intestinal perforation (1 patient). The patient Grade 4 hypokalemia (shown) also experienced Grade 4 increased blood uric acid.

(iii) Patients were assigned to toxicity grade categories based on the highest grade of AE experienced. One patient also had a fatal SAE, and therefore was counted under patients experiencing Grade 5 events. Therefore, the total number of patients experiencing Grade 4 AEs in this treatment arm was one less (7) than can be obtained by adding up the number of patients (n=8) experiencing the individual Grade 4 AEs (see footnote “ii”).

Serious Adverse Events (SAEs) (BRF113220)

The two most frequent SAEs (and drug-related SAEs) in the combination therapy arm were pyrexia and chills, whereas SCC/SCC of skin was the most frequently reported SAE in the dabrafenib monotherapy arm.[114; 158]

Table 65: Summary of SAEs experienced by ≥2 patients in either treatment arm in BRF113220 (All treated population, May 2012 cut-off) [114; 158]

	Trametinib + dabrafenib 150/2 N=55[a]	Dabrafenib monotherapy N=53[a]
Median follow-up time	**14.1 months**	
Any SAE, n (%)	**34 (62)**	**13 (25)**
Pyrexia	14 (25)	1 (2)
Chills	10 (18)	1 (2)
Dehydration	2 (4)	0
Ejection fraction decreased	2 (4)	0
Pneumonia	2 (4)	1 (2)
Pulmonary embolism	2 (4)	0
Renal failure acute	2 (4)	0
SCC	2 (4)	3 (6)
Abdominal pain	1 (2)	1 (2)
Hyponatremia	1 (2)	0
Anemia	0	1 (2)
Keratoacanthoma	0	2 (4)
SCC of skin	0	4 (8)

a. One patient randomised to the dabrafenib monotherapy arm received trametinib + dabrafenib combination therapy (150/2) (n=55) due to a dispensing error.

AEs of Special Interest (BRF113220)

AEs of special interest (AESI) comprised events that are either known class effects, were identified pre-clinically or in prior clinical studies, or are potentially life threatening (Table 66).[114] These have been discussed in more detail earlier in this section in relation to AESIs in the phase III COMBI-d and COMBI-v studies.

The incidence of cutaneous squamous cell carcinoma (including keratoacanthoma) categorised as an AESI (a co-primary endpoint in the study) was higher in patients receiving dabrafenib monotherapy compared with combination 150/2 therapy (19% vs. 7%).[25]

Table 66: AEs of special interest in either treatment arm in BRF113220 (All treated population, May 2012 cut-off)[25; 114]

	Trametinib + dabrafenib 150/2 N=55[a]	Dabrafenib monotherapy N=53[a]
Median follow-up time	**14.1 months**	
AEs of Special Interest Categories[b], n (%)		
Pyrexia	42 (76)	17 (32)
Cardiac-related events	5 (9)	0
Hepatic events	8 (15)	2 (4)
Ocular events	14 (25)	8 (15)
cuSCC (including keratoacanthoma)	4 (7)	10 (19)

New primary melanoma	0	1 (2)
Other treatment-emergent malignancies	1 (2)	0
Skin-related toxicities	36 (65)	36 (68)
Diarrhoea	20 (36)	15 (28)

a. One patient randomised to the dabrafenib monotherapy arm received trametinib + dabrafenib combination therapy (150/2) (n=55) due to a dispensing error.

b. PPES and uveitis are AEs of special interest for dabrafenib monotherapy. In the present analysis, these terms have been incorporated under the "Skin-related toxicities" and "Ocular Events" categories, respectively, and not reported separately.

Note: There were no reports of pneumonitis in any treatment group.

4.12.2.2.3 Dose modifications due to AEs (BRF113220)

AEs leading to permanent treatment discontinuation (BRF113220)

A higher proportion of patients in the combination 150/2 arm permanently discontinued dabrafenib and/or trametinib due to AEs compared with those subjects receiving dabrafenib monotherapy (Table 67).[114]

Table 67: AEs leading to permanent discontinuation of study drug in either treatment arm in BRF113220 (All treated population, May 2012 cut-off)[114]

	Trametinib + dabrafenib 150/2 N=55[a]	**Dabrafenib monotherapy N=53[a]**
Median follow-up time	**14.1 months**	
Any AE, n (%)	**5 (9)**	**1 (2)**
Pyrexia	2 (4)	0
Cerebral haemorrhage	1 (2)	0
Dyspnoea	1 (2)	0
Fatigue	1 (2)	0
Nausea	1 (2)	0
Renal failure	1 (2)	0
Blood creatinine increased	0	1 (2)

a. One patient randomised to the dabrafenib monotherapy arm received trametinib + dabrafenib combination therapy (150/2) (n=55) due to a dispensing error.

AEs leading to dose interruptions or dose reductions (BRF113220)

Similar to the COMBI-d and COMBI-v studies, the most common AEs leading to dose interruption or dose reduction in BRF113220 included pyrexia, chills and decreased ejection fraction (Table 68 and Table 69). Re-escalation of the dose was possible in the majority of patients.[25; 114]

Table 68: AEs leading to dose interruption in ≥3% of patients in either treatment arm in BRF113220 (All treated population, May 2012 cut-off) [25; 114]

	Trametinib + dabrafenib 150/2 N=55[a]	Dabrafenib monotherapy N=53[a]
Median follow-up time	**14.1 months**	
Any AE, n (%)	**37 (67)**	**18 (34)**
Pyrexia	23 (42)	3 (6)
Chills	12 (22)	3 (6)
Ejection fraction decreased	5 (9)	0
Arthralgia	4 (7)	0
Diarrhoea	4 (7)	2 (4)
Fatigue	4 (7)	1 (2)
Nausea	4 (7)	1 (2)
Neutropenia	4 (7)	1 (2)
Vomiting	4 (7)	0
Myalgia	3 (5)	0
Dehydration	2 (4)	0
GGT increased	2 (4)	0
Headache	2 (4)	0
Hyponatraemia	2 (4)	0
Renal failure acute	2 (4)	0
Atrial fibrillation	1 (2)	2 (4)

a. One patient randomised to the dabrafenib monotherapy arm received trametinib + dabrafenib combination therapy (150/2) (n=55) due to a dispensing error.

GGT = Gamma glutamyl transferase.

Table 69: AEs leading to dose reduction in ≥2 patients in either treatment arm in BRF113220 (All treated population, May 2012 cut-off)[25; 114]

	Trametinib + dabrafenib 150/2 N=55[a]	Dabrafenib monotherapy N=53[a]
Median follow-up time	**14.1 months**	
Any AE, n (%)	**27 (49)**	**11 (21)**
Pyrexia	19 (35)	2 (4)
Chills	5 (9)	1 (2)
Nausea	5 (9)	0
Ejection fraction decreased	4 (7)	0
Vomiting	4 (7)	0
Diarrhoea	2 (4)	1 (2)
Myalgia	2 (4)	0
Arthralgia	1 (2)	0
Fatigue	1 (2)	0
Infleunza-like illness	1 (2)	1 (2)

a. One patient randomised to the dabrafenib monotherapy arm received trametinib + dabrafenib combination therapy (150/2) (n=55) due to a dispensing error.

4.12.3. Provide details of any studies that report additional adverse reactions to those reported in section 4.2. Include the following.

No studies were identified in the systematic review that report additional safety data to those available from the COMBI-d, COMBI-v and BRF113220 (Part C) studies as detailed above.

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

The safety profile of trametinib + dabrafenib combination therapy has been established in RCTs involving nearly 1,300 patients[17; 18; 19; 20; 25] and generally reflects the safety profiles of the individual agents.[14; 41] The pattern and incidences of AEs associated with the combination is consistent across the Phase III COMBI-d and COMBI-v studies, and the Phase II BRF113220 (Part C) study.[17; 18; 19; 20; 25; 26] The most common AEs (occurring in ≥ 20 % patients) for trametinib + dabrafenib combination therapy include: pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, and vomiting.[21; 22] No new or unexpected safety concerns have emerged with longer exposure/follow-up times in any of the studies.[30; 20]

Approximately half of all the AEs experienced by patients on combination treatment were Grades 1 and 2. Grade 3/4 AEs occurred in 45% and 57% of patients on combination therapy in the Phase III studies (compared with 50% and 66% on dabrafenib and vemurafenib monotherapy respectively). Pyrexia and hypertension were the most common Grade 3 events experienced on combination therapy.[37]

Pyrexia appears to be a specific toxicity of dabrafenib treatment [86] and the incidence is increased for combined trametinib + dabrafenib therapy compared with dabrafenib monotherapy (52% vs. 25% for treatment-related pyrexia in the COMBI-d study[18]). However, as discussed earlier, most episodes of pyrexia are manageable with anti-pyretic medication and/or temporary interruption of dabrafenib treatment.[17; 19] There were no Grade 4 pyrexia events associated with combination therapy in any of the studies and ≤4% of patients discontinued treatment due to pyrexia.[18; 20; 25]

Although the addition of trametinib to dabrafenib results in an increase in the incidence of some AEs relative to the monotherapies (most notably pyrexia), skin-related toxicities (e.g. hyperkeratosis, hand-foot syndrome/PPE, alopecia, cuSCCs and new primary melanomas) have been observed at a reduced frequency and with a delayed time to onset in patients receiving the combination compared with dabrafenib or vemurafenib alone.[17; 18; 19; 20] Nevertheless, regular skin examinations are advised in patients receiving trametinib + dabrafenib combination therapy and for up to 6 months after discontinuation.[21; 22]

Analysis of AEs in COMBI-v with a ≥10% difference in incidence between treatment arms sorted by risk difference has highlighted key differences in the AE profile of trametinib + dabrafenib combination therapy compared with that of vemurafenib monotherapy (Figure 25). A higher risk of pyrexia, chills, and vomiting were found in the combination arm; and a higher risk of skin-related toxicities, sunburn, photosensitivity reactions, arthralgia, and alopecia in

the vemurafenib arm.[113] The impact of these conditions for patients is discussed in the next section (4.13.1).

Decreased ejection fraction has previously been associated with the use of MEK inhibitors[41] and occurred in 6-8% of patients receiving trametinib in addition to dabrafenib in the Phase III studies (compared with 3% and <1% of those on dabrafenib and vemurafenib alone, respectively). The majority of the LVEF decreases that met interruption criteria were asymptomatic and resolved. Most subjects who were re-challenged were able to continue on treatment without further dose modification. These findings suggest that regular LVEF monitoring as specified on the trametinib SPC with appropriate dose modification may prevent more severe sequelae.

Ocular toxicities have been observed during monotherapy with either BRAF or MEK targeted agents; specifically uveitis has been infrequently associated with BRAF inhibitors while retinal events (e.g. chorioretinopathy, retinal detachment) have been seen uncommonly with MEK inhibitors.[41; 159; 160] Such events were each reported in ≤1% of patients in the combination arms of both Phase III studies, and there were no reports of retinal vein occlusion in either study[111; 113] Patients should be monitored for visual changes/symptoms while on trametinib + dabrafenib combination therapy[21; 22] and referred to ophthalmology for review if required.

The discontinuation rate due to AEs for the trametinib + dabrafenib combination was 9-16% across the clinical studies, indicating that the majority of patients were able to remain on therapy.[20; 30] This is supported by the rates of dose reduction (~30%) and temporary interruptions (~50%) due to AEs[20, 30], enabling patients with significant AEs to be managed through dose modification thereby avoiding permanent cessation of treatment. The most common AE leading to dose modification on combination therapy was pyrexia (compared to rash on vemurafenib monotherapy).[111; 113]

In summary, the combination regimen of trametinib 2mg o.d. + dabrafenib 150mg b.d. has a well-characterised safety profile that is manageable with appropriate interventions as specified on the SPCs. As discussed in section 2.4, the resource requirements for monitoring patients and managing AEs associated with trametinib + dabrafenib combination therapy are unlikely to differ significantly from those currently associated with the use of BRAF inhibitor monotherapies.

4.13. Interpretation of the clinical effectiveness and safety evidence

When concluding the clinical effectiveness and safety evidence, provide the information specified in sections 4.13.1 and 4.13.2.

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

<u>Clinical benefits of trametinib + dabrafenib combination therapy</u>

(i) Efficacy benefits

The efficacy benefits provided by trametinib + dabrafenib combination therapy compared with dabrafenib or vemurafenib administered as monotherapy in patients with BRAF V600

mutation-positive unresectable or metastatic melanoma is summarised in Table 70 and discussed below:

Overall survival (OS)

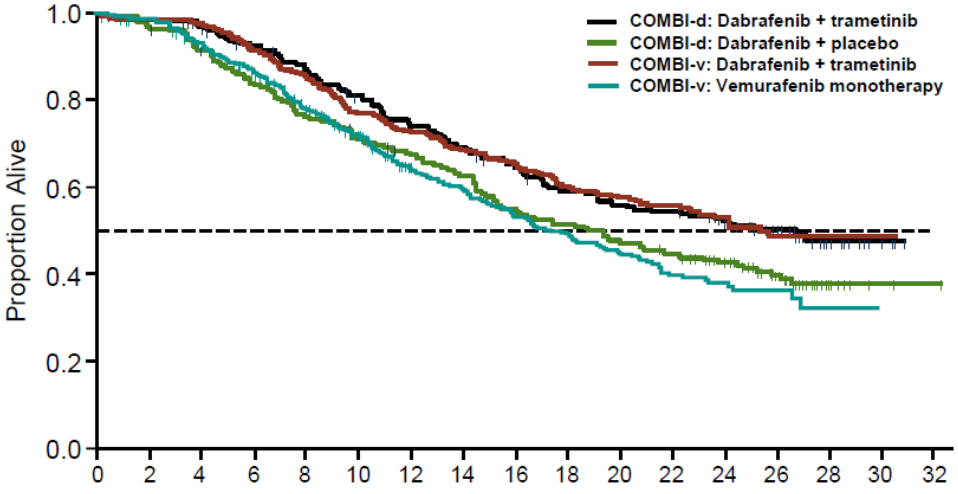
The two Phase III studies, COMBI-d and COMBI-v, demonstrate that the addition of trametinib to dabrafenib confers a statistically significant and clinically meaningful reduction in the risk of death compared with BRAF inhibitor monotherapy. The pre-planned final OS analysis of COMB-d (January 2015 cut-off; median follow-up time: 20 months) demonstrated a 29% reduction in risk of death for the combination compared with dabrafenib monotherapy. Median OS for the combination therapy (25.1 months) was approximately 6 months longer than that for dabrafenib monotherapy (18.7 months).[18]

The latest OS analysis of COMBI-v (March 2015 cut-off; median follow-up time 19 months) found a 34% reduction in the risk of death. Median OS was 25.6 months in the combination arm, 7.6 months longer than that in the vemurafenib arm (18.0 months).[20] By this time, 21 (6%) patients originally randomised to vemurafenib had switched to receive trametinib + dabrafenib which may have impacted the OS gain. Adjustment for crossover using the RPSFT 'treatment group' model yielded an adjusted HR of 0.63 (95% CI: 0.50, 0.79) for the combination versus vemurafenib monotherapy.[27]

In both COMBI-d and COMBI-v, a greater percentage of patients on the BRAF inhibitor monotherapy arms received subsequent anti-cancer treatments after cessation of study medication (including higher usage of the immunotherapy, ipilimumab, known to positively impact survival in metastatic melanoma[6]) compared with the combination arms, indicating that the OS advantage of the combination is not attributable to more post-study therapy.[18; 19]

The Kaplan-Meier OS curves for combination therapy and BRAF inhibitor monotherapy separate early (within 3 months) and remain separated (Figure 26). Additionally, the curves representing the combination arms from the two studies track closely with each other as do the curves for the dabrafenib and vemurafenib arms, illustrating the consistency of the OS results across the studies Indeed, the CHMP has acknowledged that the OS data for combination therapy from the two studies are comparable to each other.[37] The OS rates at 1-year and 2-years for the trametinib + dabrafenib combination are also very similar between the studies and longer than those for the monotherapies (73-74% vs. 64-68% at 1 year; 51% vs. 38-42% at 2 years).[18; 20]

Figure 26: Graph of Kaplan Meier curves for COMBI-d (January 2015 cut-off) and COMBI-v (March 2015 cut-off)[19]



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

The survival results of the COMBI-d and COMBI-v studies are supported by updated OS analyses from the BRF113220 Phase II study. The latest median OS for combination therapy (25.0 months) is consistent with the medians observed in the Phase III studies and has not changed with additional follow-up time. This was not significantly different from the dabrafenib monotherapy arm (median 20.2 months), largely due to the high proportion of patients randomised to the monotherapy (45/54; 83%) who crossed over to receive the combination after independently-confirmed disease progression.[26] The RPSFTM-adjusted HR of 0.55 (95% CI: 0.20, 1.55) indicates a clinically relevant reduction in risk of death for trametinib + dabrafenib combination therapy versus dabrafenib monotherapy. The point estimate for the OS HR has improved even though the confidence interval remains wide due to the methodology employed.[118] The 1-year and 2-year OS rates for the combination arm in BRF113220 were similar to those in the Phase III studies; the longer follow-up time (~46 months at January 2015 cut-off) has provided a 3-year OS estimate for the combination of 38%.[26]

Table 70: Primary & secondary efficacy endpoints in COMBI-d, COMBI-v and BRF113220 (Part C) (ITT populations)

Endpoint		COMBI-d (MEK115306)[18] Latest cut-off: 12 January 2015		COMBI-v (MEK116513)[20] Latest cut-off: 13 March 2015		BRF113220 (Part C)[25; 26] PFS cut-off: 31 May 2012 Latest OS update: 15 January 2015	
		Key evidence, Phase III RCTs				Supportive evidence, Phase II RCT	
		Trametinib + dabrafenib N=211	Dabrafenib monotherapy N=212	Trametinib + dabrafenib N=352	Vemurafenib monotherapy N=352	Trametinib + dabrafenib (150/2) N=54	Dabrafenib monotherapy N=54
Median follow-up time, months		20.0	16.0	19.0	15.0	14.1 (PFS cut-off); ~46 (latest OS cut-off)	
Progression-free survival (Primary endpoint in COMBI-d and BRF113220)	Median, months (95% CI)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	12.6 (10.7, 15.5)	7.3 (5.8, 7.8)	9.4 (8.6, 16.7)	5.8 (4.6, 7.4)
	HR (95% CI) p-value	0.67 (0.53, 0.84) p=0.0004		0.61 (0.51, 0.73) p<0.001		0.39 (0.25, 0.62) p<0.001	
Overall survival (Primary endpoint in COMBI-v)	Median, months (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	25.6 (22.6, NR)	18.0 (15.6, 20.7)	25.0 (17.5, 36.5)	20.2 (14.5, 27.1)
	HR (95% CI) p-value	0.71 (0.55, 0.92) p=0.011		0.66 (0.53, 0.81) p<0.001		0.77 (0.49, 1.21) p=NS	
	1-year OS % (95% CI)	74 (67, 79)	68 (61, 74)	73 (68, 77)	64 (59, 69)	80 (66, 88)	70 (56, 81)
	2-year OS % (95% CI)	51 (44, 58)	42 (35, 49)	51 (45, 57)	38 (32, 44)	51 (37, 64)	44 (31, 57)
	% crossover	Not applicable		21 / 352 (6%)		45 / 54 (83%)	
	RPSFTM-adjusted HR (95% CI)	Not applicable		0.63 (0.50, 0.79)		0.55 (0.20, 1.55)	
Overall response rate	ORR (CR + PR), n (%) (95% CI)	144 (69%) (61.8, 74.8)	112 (53%) (46.3, 60.2)	231 (66%) (60.4, 70.6)	186 (53%) (47.5, 58.2)	41 (76%) (62.4, 86.5)	29 (54%) (39.6, 67.4)
	p-value	p=0.0014		p=0.0008		p=0.0264	
Duration of response	Median, months (95% CI)	12.9 (9.4–19.5)	10.6 (9.1–13.8)	13.8 (11.2-18.1)	8.5 (7.4-9.7)	10.5 (7.4, 14.9)	5.6 (4.5, 7.4)

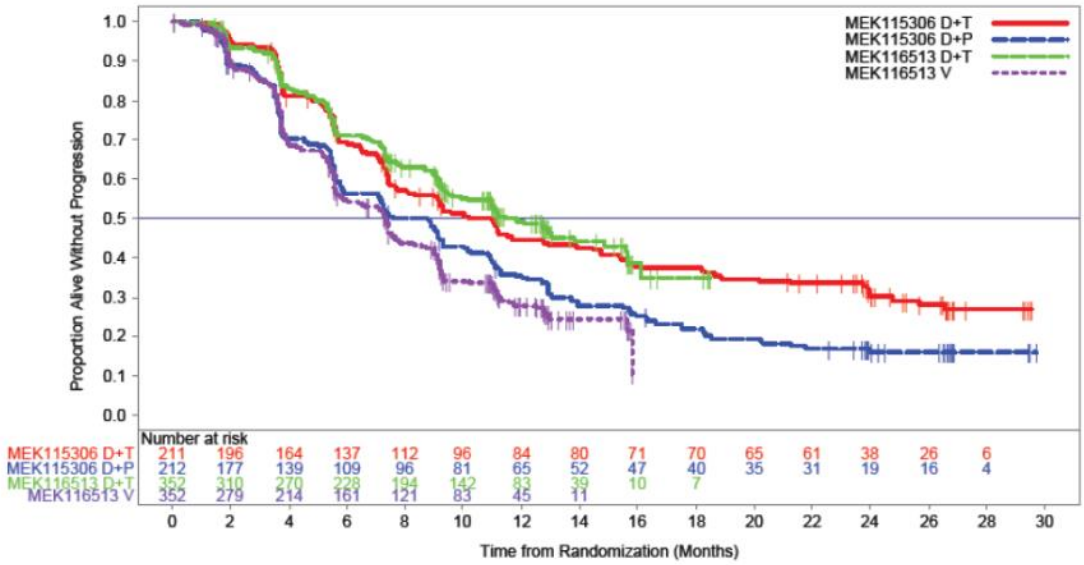
Progression-free survival (PFS)

The two Phase III studies also show similar statistically significant and clinically meaningful reductions (of at least 33%) in the risk of tumour progression or death for trametinib + dabrafenib combination therapy compared with dabrafenib or vemurafenib as monotherapies.

Figure 27 illustrates the similar trajectories of the Kaplan-Meier PFS curves for the combination and BRAF inhibitor monotherapy arms in the two studies.

The updated analysis in COMBI-v (March 2015 cut-off) yielded a median PFS for the combination arm of 12.6 months compared with 7.3 months for the vemurafenib arm, which is similar to previous estimates for vemurafenib monotherapy.[15] Median PFS at the latest data cut in COMBI-d (January 2015 cut-off) was longer in the trametinib + dabrafenib group (11.0 months) than in the dabrafenib group (8.8 months).[18] This latter median is greater than those observed for dabrafenib monotherapy in previous studies.[14; 25] This disparity may be attributable to the natural variation in single-point estimates across different studies. As can be seen in Figure 27, there is a "step" in the dabrafenib monotherapy curve which traverses the median – if a few more patients had experienced progression before 8.8 months, the median value would have been substantially lower and more similar to that achieved in the control arm in COMBI-v. The BRF113220 study provides supportive results for the PFS benefit of trametinib + dabrafenib combination therapy over dabrafenib alone.[25]

Figure 27: Graph of Kaplan Meier curves for COMBI-d (January 2015 cut-off) and COMBI-v (April 2014 cut-off)[37]



Overall response rate (ORR) and Duration of response (DoR)

In both Phase III studies, the investigator-assessed confirmed ORRs (per RECIST v1.1) were high and significantly greater in the combination arms compared with the BRAF inhibitor monotherapy arms (66-69% vs. 53%) [18; 20], indicating that a large proportion of patients obtain at least a 30% reduction in tumour burden. Complete response (CR) rates

(disappearance of all target lesions) of 16-17% were observed for combined trametinib + dabrafenib therapy versus 10-13% for the monotherapies. Tumour responses achieved with the combination were also durable (medians of 12.9 months and 13.8 months reported in COMB-d and COMBI-v, respectively).[18; 20] Investigator-assessed ORR results from BRF113220 were consistent with those achieved in the COMBI studies.[25]

Subgroups

Subgroup analyses of COMBI-d and COMBI-v demonstrate that PFS and OS were longer with the combination than with dabrafenib or vemurafenib monotherapy in all subgroups examined. These findings indicate that the combination is more effective than BRAF inhibitor monotherapy regardless of mutation type, gender, age, performance status, baseline LDH and other prognostic factors and support trametinib + dabrafenib combination treatment for all adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.[18; 20]

Health-related quality of life (HRQoL)

HRQoL can be negatively impacted for patients with metastatic melanoma.[8; 64; 65] Improving HRQoL is therefore an important consideration, particularly as treatment is not curative in the majority of patients.[28] Results of the HRQoL analyses (based on the EORTC-QLQ-C30 and EQ-5D questionnaires in both COMBI-d and COMBI-v, and additionally the FACT-M Melanoma Subscale in COMBI-v) show that the improvements in PFS, OS and ORR achieved with the combination equate to a real and substantial HRQoL advantage for the patient. In COMBI-d, global health status was consistently better for patients receiving trametinib + dabrafenib compared with those on dabrafenib monotherapy, and pain scores were significantly and clinically meaningfully improved for patients on the combination at all assessments.[28] In COMBI-v, statistically significant and clinically meaningful improvements in favour of the combination over vemurafenib were observed for global health, for physical/ role/social functioning, and in several symptoms (pain, insomnia, appetite loss and diarrhoea) at all assessments.[29] Together, these results indicate that patients receiving the combination therapy feel better than those on BRAF inhibitor monotherapy. The uniformity of the findings across all three questionnaires in COMBI-v supports the robustness of the results.[29] Trametinib + dabrafenib is the first BRAF and MEK inhibitor combination therapy to have reported consistent benefits across these HRQoL instruments.[29]

(ii) Safety benefits

It might be expected that giving two drugs in combination would lead to a higher incidence of AEs being experienced by patients than with single-agent therapy. However, the addition of trametinib to dabrafenib results in some benefits from a safety perspective compared with the administration of BRAF inhibitor monotherapy.

Cutaneous adverse events (AEs)

Of note, cutaneous AEs, particularly hyperproliferative lesions, are observed less frequently with trametinib + dabrafenib combination therapy than with BRAF inhibitor monotherapy.[17; 18; 19; 20] This is believed to be due to attenuation of BRAF-inhibitor induced paradoxical

signalling along the MAPK pathway by trametinib.[25] Importantly, new malignancies, such as cuSCCs which might be alarming to patients, occurred in at least a third fewer subjects receiving trametinib + dabrafenib than those on BRAF inhibitor monotherapy (3% vs. 10%, COMBI-d[37]; 2% vs. 19% COMBI-v[20]). In addition, hand-foot syndrome which can be debilitating for patients and greatly impact on their quality of life[161]; alopecia, whilst neither life-threatening nor painful can be a distressing condition for those who experience it[162]; hyperkeratosis and skin papillomas were all less common with trametinib + dabrafenib combination therapy than with BRAF inhibitor monotherapy. The frequency of rash (and rash-like conditions) was similarly reduced; this was particularly evident in the COMBI-v study where the incidence of rash was almost twice as high in the vermurafenib arm compared with the combination arm (including a higher rate of G3 events).[20]

Vemurafenib is known to cause a marked increase in sensitivity to sunlight, manifesting as adverse events of photosensitivity and sunburn.[15; 48] Phototoxicity in patients receiving vemurafenib can develop despite minimal UV exposure[163], and may cause considerable morbidity. It can have a significant impact on patients' quality of life[48; 49; 164], especially for those who spend time outdoors or driving, and requires strict sun avoidance/protection measures such as wearing UV-dense clothing regardless of daylight or season and using broad spectrum sun screen and lip balm of at least SPF ≥ 30.[40] It is therefore a clinical benefit that photosensitivity and sunburn was reported at a lower rate in patients treated with trametinib + dabrafenib than those on vemurafenib (4% vs. 23%; 1% vs. 15% respectively).[20]

Musculoskeletal disorders

Arthralgia is a troublesome side effect of many anti-cancer therapies and can cause marked discomfort and impact activities of daily living.[165] Arthralgia was approximately half as frequent for patients receiving trametinib + dabrafenib combination therapy than for those on vemurafenib monotherapy (27% vs. 52%) in the COMBI-V study.[20]

<u>Harms of trametinib + dabrafenib combination therapy</u>

Pyrexia

The most notable harm associated with trametinib + dabrafenib combination therapy is pyrexia which occurred in approximately 60% of patients in the Phase III clinical studies.[18; 20] However, most pyrexia events associated with the combination were Grade 1 or 2; ≤7% of patients had grade 3 pyrexia events and there were no Grade 4 events. Pyrexia events tend to occur early in the course of treatment (first occurrence within median 30-40 days) and are short-lived (median 3 days duration). Of those experiencing pyrexia events in the clinical studies, at least one half of patients had no more than 1 or 2 events.

None of the HRQoL questionnaires used in the Phase III studies included items that directly referred to pyrexia; however, if fever had a negative effect on HRQoL, it would have been observed on domains such as global health or functioning (e.g. physical or role functioning) which was not the case.[28; 29] The majority of dose interruptions (~60%) in the COMBI studies were attributable to pyrexia[20; 37] (consistent with protocol-specific guidance on its management) yet the discontinuation rate due to pyrexia was low (≤4%).[18; 20] This suggests

that this AE only significantly impacts a small minority of patients and most are able to resume treatment following temporary interruption.

MEK-inhibitor induced events

Acneiform dermatitis is one of the most common toxicities associated with trametinib. Although more prevalent with trametinib + dabrafenib combination therapy than with dabrafenib monotherapy[37], its incidence appears to be reduced compared to single-agent trametinib.[25; 41] Additional recognised class effects of MEK inhibitors include ocular conditions and cardiac events.[41] A decrease in ejection fraction was more frequent with combination therapy than with BRAF inhibitor monotherapy (all-grade, all-cause: 6% vs. 3% in COMBI-d; 8% vs. <1% in COMBI-v), though the majority of cases were asymptomatic and reversible.[37; 20] The incidence of ocular events (chorioretinopathy, retinal detachment) was low (≤1%) and similar between the trametinib + dabrafenib combination and dabrafenib or vemurafenib monotherapy. Other MEK-inhibitor associated AEs such as oedema and pneumonitis occurred at a frequency consistent with the known AE profile of trametinib. None of these events occurred with a Grade 4 severity in the Phase III studies.[37]

Summary of clinical benefits

The two Phase III (COMBI-d, COMBI-v) and supportive Phase II (BRF113220) RCTs provide clear evidence of the clinical benefits provided by trametinib + dabrafenib combination therapy over BRAF inhibitor monotherapy in prolonging PFS, achieving high response rates, and extending survival in patients with BRAF V600 mutation-positive metastatic melanoma. The efficacy superiority of the combination has been seen in all subgroups examined and also translates into major improvements in patient-perceived HRQoL. These clinical outcomes substantiate the pre-clinical findings that more complete blockade of the oncogenic MAPK pathway via both BRAF and MEK kinases through combining trametinib with dabrafenib can attain greater anti-tumour activity than either drug alone.

The reduction in cutaneous events seen with the combination compared with BRAF inhibitor monotherapy confirms the premise that the addition of trametinib can abrogate a safety concern of BRAF inhibitors resulting from their paradoxical activation of the MAPK pathway. Other patient-important AEs are also less frequent with trametinib + dabrafenib therapy compared with vemurafenib monotherapy. This combination therefore offers an acceptable and potentially preferable safety profile for patients with BRAF V600 mutation-positive metastatic melanoma. Together these efficacy and safety benefits mean that the combination of trametinib + dabrafenib represents a significant treatment advance over single-agent BRAF inhibitors for this small patient population suffering from this aggressive disease.

4.13.2. A discussion of the strengths and limitations of the clinical evidence base for the technology. This should include the following:

4.13.2.1. A brief statement on the internal validity of the studies included in the clinical evidence base.

Internal validity of the trials

The evidence for trametinib + dabrafenib combination therapy versus the comparators, dabrafenib and vemurafenib as monotherapy, comes from three randomised controlled trials – two large Phase III RCTs (COMB-d [MEK115306] and COMBI-v [MEK116513]) and a supportive Phase II RCT (BRF113220 [Part C]). [17; 18; 19; 20; 25] These studies were all well-conducted and methodologically robust.

Sample size and power

The Phase III studies were designed with 90% power to detect a difference between treatment arms in their primary efficacy endpoints.[17; 19] COMBI-d was originally planned to recruit 340 patients but over-recruited by 24% (423 patients actually enrolled); it was therefore decided to perform the primary PFS analysis after 193 events (instead of 155 progression events) which resulted in an increase in power from 90% to 95%.[37]

Blinding and accounting for bias

COMBI-d was a double-blind study with blinding through the use of matching trametinib placebo tablets; great efforts were taken to maintain the blinding until the final OS analysis. COMBI-v and BRF113220 were both open-label studies which may have biased collection of the outcome data. Overall survival was the primary endpoint in COMBI-v which is unambiguous to measure and not subject to investigator interpretation.[128] Any negative effect of the open-label nature in BRF113220 may have been lessened by the inclusion of a Blinded Independent Review Committee (BIRC) to independently assess disease response and progression. COMBI-d also included a blinded review of scans to assess progression and response until the initial data-cut in August 2013. The BIRC analysis identified fewer progression events than the investigators' assessments and showed approximately 20% discordance, but did not suggest a bias in the assessments made by the investigators. Additional sensitivity analyses of PFS (such as utilising symptomatic progression as an event) were performed in all three studies to demonstrate the robustness of the treatment effect on PFS; the HRs reported were consistent with those for the primary investigator-assessed PFS analyses.[25; 37; 111]

The over-enrolment in COMBI-d was expected to induce more censorings and therefore bias in the estimation of the PFS median in the combination arm if the original timing (155 events) was retained. The timing was therefore changed proportionally so that the primary PFS analysis was to be performed after 193 events, thereby maintaining the same ratio of events to patients as originally planned (46.5%).[37]

Crossover

RCTs in the late-stage cancer setting frequently incorporate a ‘crossover’ so that patients in the control arm have the opportunity to benefit from the investigational treatment once their disease has progressed. This often leads to confounding of the OS results by improving survival times for the control group.

For this reason, COMBI-d did not allow crossover in order to maintain the integrity of OS as an end point. Similarly, crossover was originally prohibited in COMBI-v but was permitted following a planned interim analysis which crossed the pre-specified boundary for efficacy.[19] The study was stopped early and a protocol amendment permitted patients in the vemurafenib arm to switch to receive trametinib + dabrafenib, irrespective of whether or not they had progressed.[20] As of the March 2015 cut-off, 21 (6%) patients in the control arm had switched, 15 of them before progression on vemurafenib, which may have impacted the OS benefit attributable to the combination.[27]

For ethical reasons, BRF113220 was designed to allow patients who experienced disease progression on the control arm to switch to receive the investigational treatment. More than 80% of patients randomised to dabrafenib monotherapy had crossed over to receive the combination at the last data cut (January 2015), but only after progression, which has likely attenuated the true OS effect of trametinib + dabrafenib treatment.

The optimal method to adjust for the confounding effects of crossover remains an area of academic debate, and several methodologies were considered in relation to the COMBI-v and BRF113220 OS data. The Rank Preserving Structural Failure Time Model (RPSFTM) was deemed to be the most appropriate for these data sets (see Section 4.4.3.2).[27; 118] This is a respected statistical methodology that has been accepted by NICE in previous appraisals.[81; 82; 147]

Follow-on systemic anti-cancer therapy

Alternative anti-cancer therapy at cessation of study treatment was at the discretion of investigators. More subjects in the BRAF inhibitor monotherapy arms received subsequent systemic anti-cancer medication than in the combination arms (including higher usage of ipilimumab), indicating that any imbalance in follow-on therapy between treatment arms has not influenced OS in favour of the combination.

Randomisation and patient balance in treatment arms

Patients in all three RCTs were centrally randomised through an interactive voice response system (IVRS) using a computer generated randomisation schedule.

This resulted in the treatment arms in all three RCTs being generally well matched for demographic and disease characteristics at baseline. The COMBI-d and COMBI-v studies were stratified for mutation type (V600E and V600K) and baseline LDH (LDH≤ULN versus LDH >ULN) and these factors were also well balanced between treatment arms.[17; 20] Additionally, as acknowledged by the CHMP, the patient populations in the two studies were comparable and any minor imbalances between treatment arms did not affect the reliability of the study results.[37]

Health-related quality of life (HRQoL) assessments

Analysis of HRQoL data are frequently limited by missing data especially at later time points. This was not the case in COMBI-d and COMBI-v; completion rates for the HRQoL questionnaires were very good in both studies (≥80% at all assessments until week 40 [COMBI-d] and week 56 [COMBI-v], and >70% at the disease progression visit in both studies).[28] It should be noted, however, that the studies were not powered for the HRQoL endpoints and there were no HRQoL *a priori* hypotheses, therefore all the HRQoL results should be considered exploratory.[29] The HRQoL results in COMBI-d are strengthened by the fact it was a double-blind study and thus responses are reflective of how patients truly felt[28], whereas in COMBI-v patient's expectations about their treatment efficacy may have affected their responses since it was an open-label study.[29]

A fuller discussion of the endpoints employed in these studies is provided in the next section.

Other methodological factors

Reasons for withdrawal were adequately documented in all the studies and efforts were made to follow subjects who prematurely withdrew due to reasons other than progressive disease or death. An ITT analysis was used for the efficacy endpoints in all three studies and appropriate methods were used to account for missing data.

4.13.2.2 A brief statement on the external validity of the studies included in the clinical evidence base. Include the relevance of the evidence base to the decision problem and the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice. Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

<u>(i) External validity of trials and applicability of the evidence to routine clinical practice</u>

No major factors relating to the trial populations or procedures have been identified that would negatively influence the applicability of the evidence for trametinib + dabrafenib to patients likely to receive this treatment in routine clinical practice in England. There were 17 UK study centres in the Phase III COMBI-d and COMBI-v studies, which enrolled a total of 72 patients between them. There were no UK centres in the Phase II BRF113220 (Part C) study.

Trial populations versus clinical practice

We consider the demographic and disease characteristics of participant patients in these RCTs to be representative of patients with BRAF mutation-positive unresectable or metastatic melanoma that would receive treatment with trametinib + dabrafenib in clinical practice in England.

Patients in the studies had a mean age of 52 to 55 years. The mean age of diagnosis of malignant melanoma in the UK is cited as being around 50 years[53], but this is for all melanoma irrespective of disease stage and BRAF mutation status. There are no UK data specifically available for the mean age of diagnosis of BRAF V600 mutation-positive

metastatic melanoma, though an Australian study has put this at 56 years.[10] The characteristics of patients in the RCTs in terms of gender, ECOG performance status and baseline LDH level closely match those of a recent UK observational study in metastatic melanoma.[166] The proportions of patients in the studies with a BRAF V600E (versus BRAF V600K) mutation (~85%) and M1c stage disease (~65-70%) broadly concur with real-world studies of BRAF inhibitor therapy in metastatic melanoma that included UK centres.[167; 168]

Additionally, patients' baseline scores on the EORTC-QLQ-C30 questionnaire in COMBI-d and COMBI-v were comparable to EORTC QLQ-C30 reference values from an international sample of patients with stage III/IV malignant melanoma[169], providing further evidence that the patient population in the studies is reflective of the general population of patients with metastatic melanoma.

Trial methodologies versus clinical practice

Patients were selected for the clinical studies using BRAF testing, which is routinely used to screen for the presence of a BRAF mutation in metastatic melanoma patients in clinical practice in England.

Study treatment was initiated at the full licensed dose for both dabrafenib and trametinib, in line with the marketing authorisations. Dose interruptions to manage AEs were undertaken in approximately 55% of patients receiving combination therapy in the phase III studies, and dose reductions in approximately 30%, consistent with the way that the drug should be utilised in clinical practice. During the trials, subjects received full supportive care in accordance with their institutional guidelines including treatment with antibiotics, anti-emetics, anti-diarrhoeals, anti-pyretics, analgesics and any other care as deemed appropriate. It is likely that patients eligible for the combination of trametinib + dabrafenib in clinical practice will require similar concomitant medications for the management of co-morbid conditions, adverse events, infections or other complications.

The nature and timing of assessments undertaken in the RCTs are unlikely to differ significantly from routine clinical practice. Tumour assessments were conducted every 8 weeks until week 56, and every 12 weeks thereafter.[17; 19] Patients with metastatic melanoma are likely to be scanned every 8-12 weeks in clinical practice. In the RCTs, physical examinations, dermatologic evaluations, assessment of performance status, vital signs, and chemistry and haematology tests were repeated every 4 weeks.[17; 19] This is likely to be very similar in clinical practice since patients with metastatic melanoma will be seen at clinic approximately once a month, when the necessary examinations and blood tests will be carried out.

In the RCTs, ECG and ECHO assessments were performed at baseline and repeated at week 4 and every 12 weeks thereafter; an ophthalmologic evaluation was carried out at baseline, at week 4 and as symptomatically warranted.[17; 19] The SPCs for dabrafenib and trametinib provide similar monitoring advice[21; 22], and thus, the frequency of these assessments should not be dissimilar in clinical practice.

In summary, there are no methodological / procedural issues which would render the results of the combination studies inapplicable in England. Thus, there are no reasons to believe that the clinical benefits of trametinib + dabrafenib seen in COMBI-d, COMBI-v and

BRF113220 would not translate to the patients eligible to receive the combination of trametinib + dabrafenib in English clinical practice.

(ii) Relevance of endpoints assessed to the clinical benefits experienced by patients

The goals of treatment for metastatic melanoma are to reduce tumour load, delay disease progression and extend survival whilst minimising toxicity and detriment to quality of life.[28; 59] The outcomes assessed in the clinical studies of trametinib + dabrafenib combination therapy are consistent with these goals, and thus, highly relevant to the clinical benefits that should be expected for patients with metastatic melanoma in England.

Progression-free survival (PFS)

PFS was the primary endpoint in COMBI-d and BRF113220. In the latter study, patients were able to crossover from the dabrafenib control arm to receive combination treatment upon progression, thereby confounding the OS endpoint.

With PFS, the treatment effect is not diluted by crossover or post-study therapy and it informs on both tumour shrinkage and disease stabilisation[139], making it particularly suitable for assessing the efficacy of targeted agents.

A recent meta-analysis of RCTs in metastatic melanoma (which included dacarbazine in the control arm and therapies such as dabrafenib, vemurafenib and ipilimumab in the investigational arms) showed that PFS is significantly correlated with OS. When all 12 studies were included (n=4,416), correlation coefficients were 0·71 (95% CI: 0·29, 0·90) with a random-effects assumption, 0·85 (95% CI: 0·59, 0·95) with a fixed-effects assumption, and 0·89 (95% CI: 0·68, 0·97) with sample-size weighting. A sensitivity analysis restricted to Phase III studies strengthened the weighted correlation coefficient to 0·93 (95% CI: 0·74, 0·98). Similarly, in 9 studies that did not permit crossover, the weighted correlation coefficient improved (0.96 [95% CI: 0.81, 0.97]), whereas inclusion of trials with >50% crossover and mature follow-up data produced a much weaker correlation coefficient (0·55 [95% CI: 0·03, 0·84]). Overall, the range of analyses indicated a strong correlation between treatment effects on PFS and OS, and the authors concluded that PFS is a robust surrogate endpoint for OS in this cancer setting.[125]

It is therefore highly relevant that trametinib + dabrafenib combination therapy has demonstrated statistically significant and clinically meaningful PFS improvements versus BRAF inhibitor monotherapy, the current standard of care. In the Phase III studies, the risk of disease progression or death was reduced by at least 33%, and the combination arms showed prolonged PFS medians in the range of 11.0 to 12.6 months.[18; 20] All sub-groups examined also showed a PFS benefit of a similar magnitude to that seen in the overall study populations.

Overall survival (OS)

OS is universally accepted as providing a direct, precise and objective measure of the clinical benefit attributable to treatment.[128] However, as previously discussed, OS results can be difficult to interpret due to the confounding effect of further active therapy (either: via

crossover, as study treatment beyond progression, or as alternative follow-on systemic anti-cancer therapy).[170]

COMBI-v showed a significant improvement in its primary endpoint of OS for combination therapy versus vemurafenib alone, with a clinically meaningful extension to survival of 7.6 months (median 25.6 vs. 18.0 months; HR 0.66 [95% CI: 0.53, 0.81]; p<0.001; March 2015 cut-off).[20] This was despite 21 (6%) patients on vemurafenib having switched to the combination and therefore adjustment for crossover has slightly improved the OS HR (0.63 [95% CI: 0.50, 0.79] using RPSFTM; see Table 48).[27]

As explained earlier, the OS data in COMBI-d have not been affected by crossover. Patients treated with the combination gained a significant and clinically meaningful improvement in survival of at least 6 months compared with dabrafenib monotherapy (median 25.1 vs. 18.7 months; HR 0·71 [95% CI 0·55, 0·92]; p=0·011; January 2015 cut-off).[18] The OS advantage was seen in the combination arms of these two studies even though a greater percentage of subjects on BRAF inhibitor monotherapy received follow-on anti-cancer medication.[18; 20] Additionally, OS was greater with combination therapy than with the BRAF inhibitor monotherapy for all subgroups examined.

In BRF113220, the OS result numerically favoured trametinib + dabrafenib, although it was not statistically significant (median 25.0 vs. 20.2 months; HR 0.77 [95% CI: 0.49, 1.21); January 2015 cut-off); crossover of 83% of patients in the dabrafenib monotherapy am to the combination has likely reduced the treatment effect.[25] The RPSFTM-adjusted OS HR of 0.55 clearly indicates that combined trametinib + dabrafenib therapy confers a clinically relevant reduction in risk of death for patients with metastatic melanoma.[118]

Response rates

Tumour shrinkage is demonstrated by the ORR endpoint, the rates of which were high and significantly greater in patients receiving trametinib + dabrafenib combination therapy (66-76%) than those on BRAF inhibitor monotherapy (53-54%) across all three clinical studies (p<0.05).[18; 20; 25] It is highly relevant that ORRs of this order have not previously been observed with treatments for metastatic melanoma. It is also important that the responses achieved with trametinib + dabrafenib were durable with median durations of more than 1 year in the Phase III studies.[18; 20]

Health-related quality of life (HRQoL)

While HRQoL is more difficult to measure than PFS, OS or AEs, it is arguably a more relevant marker of health benefit from the patient's perspective.[171] A recent paper underlined that it is important to demonstrate a clinically meaningful improvement in HRQoL alongside any increase in PFS or OS, in order to show a real benefit for the cancer patient.[170] HRQoL was assessed in COMBI-d and COMBI-v using two validated tools: the cancer-specific EORTC QLQ-C30 and the standardised EQ-5D health status measure. To capture the specific profile of HRQoL in metastatic melanoma, COMBI-v also incorporated a melanoma-specific HRQoL Subscale of the FACT-M questionnaire.

Together, the results of these different HRQoL instruments provide a comprehensive picture of the HRQoL benefits provided by trametinib + dabrafenib combination therapy compared

with BRAF inhibitor monotherapy (encompassing overall health, functional and symptomatic improvements) [28; 29] and are highly externally valid. Combination therapy not only improves survival but also the quality of survival from the point of view of the patient. The higher proportion of patients who achieved an ORR and increased duration of response, may explain a better preservation against disease-related symptoms with the combination. The decrease in some of the BRAF inhibitor-associated and MEK inhibitor-associated AEs when the two drugs are combined may also play a positive role in patient perception of benefit.[29]

Safety and Tolerability

Tolerability is an important consideration since treatments for advanced melanoma may cause side effects that interfere with patients' quality of life and incur costs and resources to manage. Adverse events were assessed in all three RCTs according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0. The combination of trametinib + dabrafenib was found to have a manageable safety profile. The most common AEs associated with the combination were clinically manageable conditions (e.g. pyrexia, headache, nausea, vomiting, diarrhoea, hypertension), and approximately half were mild-to-moderate in severity. As previously discussed, it is particularly relevant that the incidence of skin-related toxicities (including hyperkeratosis, hand-foot syndrome/PPE, alopecia, cuSCCs and new primary melanomas) is reduced through the addition of trametinib to dabrafenib compared with using a BRAF inhibitor alone.[17; 18; 19; 20] Notably, photosensitivity, which can impact on quality of life[48; 172; 164], especially for those patients who favour an outdoors lifestyle or have to spend time in the front seat of a car, arthralgia and rash were more prevalent with vemurafenib than with the trametinib + dabrafenib combination.[19; 20] The tolerability data indicate that the majority of patients who experience AEs on the combination can be managed through dose interruption and/or reduction, and thereby remain on treatment to derive the clinical benefits described (approximately 50% of patients in the Phase III studies have received trametinib + dabrafenib combination therapy for more than 12 months to date).[20; 30]

Further discussion of the relevance of the safety evidence for trametinib + dabrafenib can be found in sections 4.12.4 and 4.13.2.1 above.

4.13.3. Provide information about the life expectancy of people with the disease or condition in England and the source of the data. Also provide information on the number of people with the particular therapeutic indication for which the technology is being appraised. If the marketing authorisation includes other therapeutic indications for the technology, provide information about the numbers of people with these diseases or conditions in England and provide the source of the data. This is to assess whether the technology may be suitable for consideration as a 'life-extending treatment at the end of life' as described in section 6.2.10 of the NICE guide to the methods of technology appraisal. Complete the table below and cross reference to where this information is found in the company submission.

As shown in the table below, trametinib + dabrafenib combination therapy offers a 'life extending treatment' at the end of life.

<table>
<tr><th>Criterion</th><th>Data available</th><th>Source of evidence</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>Median overall survival (OS) with BRAF inhibitor monotherapy, the current standard of care for patients with BRAF mutation-positive metastatic melanoma, is less than 24 months.
Median OS for dabrafenib monotherapy and vemurafenib monotherapy was 18.7 and 18.0 months, in the COMBI-d and COMBI-v studies, respectively (see below).
Median OS for dabrafenib and vemurafenib as monotherapy in the BREAK-3 and BRIM-3 trials, respectively, was less than 24 months, as follows:
<table>
<tr><th>Study</th><th>Treatment</th><th>Median OS, months (95% CI)</th></tr>
<tr><td>BREAK-3 (August 2014 cut-off)[16]</td><td>Dabrafenib monotherapy n=187</td><td>20.1 (16.7, 24.4)</td></tr>
<tr><td>BRIM-3 (August 2015 cut-off)[93]</td><td>Vemurafenib monotherapy n=337</td><td>13.6 (12.0, 15.4)</td></tr>
</table></td><td>See below for COMBI-d and COMBI-v.

Grob JJ, et al. Poster presentation at Society for Melanoma Research annual meeting 2014.[16]
Chapman PB, et al. Poster presentation at Society for Melanoma Research annual meeting 2015.[93]</td></tr>
<tr><td>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</td><td>There is robust evidence from the Phase III head-to-head RCTs that trametinib + dabrafenib combination therapy, the intervention under review, offers an extension to life of at least 6 months compared with BRAF inhibitor monotherapy.
Latest OS Combi-d (January 2015 cut-off)[18]
<table>
<tr><th></th><th>Median OS, months (95% CI)</th><th>Median OS gain, months</th></tr>
<tr><td>Trametinib + dabrafenib n=211</td><td>25.1 (19.2, NR)</td><td rowspan="2">6.4</td></tr>
<tr><td>Dabrafenib monotherapy n=212</td><td>18.7 (15.2, 23.7)</td></tr>
</table>
Latest OS Combi-v (March 2015 cut-off)[20]
<table>
<tr><th></th><th>Median OS, months (95% CI)</th><th>Median OS gain, months</th></tr>
<tr><td>Trametinib + dabrafenib n=352</td><td>25.6 (22.6, NR)</td><td rowspan="2">7.6</td></tr>
<tr><td>Vemurafenib monotherapy n=352</td><td>18.0 (15.6, 20.7)</td></tr>
</table></td><td>Long GV, et al. Lancet 2015; 38:444-51.[18]

Robert C, et al. Oral presentation at European Cancer Congress 2015. Abstract no. 3301.[20]</td></tr>
<tr><td>The treatment is licensed or otherwise indicated for small patient populations</td><td>BRAF V600 mutation-positive metastatic melanoma represents as a small patient population.
As presented in Section 3.4, the maximum number of patients covered by the therapeutic indication for trametinib + dabrafenib combination therapy (adults with unresectable or metastatic melanoma with a BRAF V600 mutation) is estimated to be 992 incident cases per annum in England.</td><td>See Table 8 in Section 3.4 for data sources for this calculation.</td></tr>
</table>

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.

Clinical studies sponsored by Novartis likely to deliver additional relevant clinical evidence for trametinib + dabrafenib combination therapy in the indication being appraised within the next 12 months are tabulated below.

Table 71: Ongoing studies of trametinib + dabrafenib in BRAF mutation-positive metastatic melanoma

Study name/ number/ acronym	Study design	Population	Intervention	Comparator(s)	Main Endpoints	Status
BRF113220; NCT01726738	Phase II, randomised, three-arm, open-label	Patients with BRAF V600E mutation-positive metastatic melanoma, with ≤1 prior chemotherapy for advanced or metastatic disease	Dabrafenib 150mg b.d. + trametinib 2mg o.d. (n=54)	Dabrafenib 150mg b.d. + trametinib 1mg o.d. (n=54) Dabrafenib 150mg b.d. (n=54)	1º: PFS, ORR, DoR, incidence of SCC, safety 2º: OS, pharmacokinetics	Ongoing for additional survival & safety analyses
COMBI-d; MEK115306; NCT01584648	Phase III, randomised, two-arm, double-blind	Patients with previously untreated, unresectable stage III or metastatic (stage IV) BRAF V600E/K mutation-positive melanoma	Dabrafenib 150mg b.d. + trametinib 2mg o.d. (n=211)	Dabrafenib 150mg b.d. plus placebo (n=212)	1º: PFS (investigator-assessed) 2º: OS, ORR, DoR, safety & tolerability Exploratory: HRQoL	Ongoing for additional survival & safety analyses
COMBI-v; MEK116513; NCT01597908	Phase III, randomised, two-arm, open-label	Patients with previously untreated, unresectable stage III or metastatic (stage IV) BRAF V600E/K mutation-positive melanoma	Dabrafenib 150mg b.d. + trametinib 2mg o.d. (n=352)	Vemurafenib 960mg b.d. (n=352)	1º: OS 2º: PFS (investigator-assessed), ORR, DoR, safety & tolerability Exploratory: HRQoL	Ongoing for additional survival & safety analyses
COMBI-BM;	Phase II,	Patients with BRAF	Dabrafenib 150mg	Not applicable	1º: Intracranial	Final data

BRF117277; NCT02039947	single-arm, open-label	mutation-positive melanoma that has metastasized to the brain (≤2 systemic treatment regimens for metastatic melanoma) (4 cohorts A-D, with or without local prior (brain) therapy, asymptomatic or symptomatic)	b.d. + trametinib 2mg o.d. (target n=120)		response (IR) rate (ITT population) 2º: IR rate by cohort, disease control rate by cohort, extracranial response (ER) rate by cohort, ORR by cohort, DoR of IR/OR/ER rates by cohort, PFS by cohort, OS by cohort, safety.	collection date for primary outcome measure Q4 2015

DoR = Duration of response; HRQoL = Health-related quality of life; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; SCC = Squamous cell carcinoma

5. Cost effectiveness

All cost-effectiveness estimates incorporate the treatment and comparators at list prices (due to existing *confidential* PAS which are in place), and are therefore not reflective of the actual cost to the NHS. The confidential PAS addendum presents results incorporating the actual or estimated drug acquisition costs incorporating the discounts.

5.1. Published cost-effectiveness studies

5.1.1. Identification of studies

A systematic review was undertaken to identify economic studies, including cost-effectiveness analyses, relevant to this decision problem.

The following databases were searched from database inception to July 2015. In addition to the database searches, bibliographies of relevant published reviews were also searched to validate the review and to ensure inclusion of all relevant evidence.

Table 72: Databases searched for the literature review

Data source	Platform
MEDLINE®	Embase.com; http://www.embase.com/
Embase®	
MEDLINE® In-Process	PubMed.com
CENTRAL	Cochrane library; http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html
NHS EED	Cochrane library

CENTRAL: Cochrane Central Register of Controlled Trials; Embase®: Excerpta Medica Database; MEDLINE®: Medical Literature Analysis and Retrieval System Online; NHS EED: Cochrane National Health Service Economic Evaluation Database

Conference abstracts were hand searched to retrieve the latest, unpublished, studies. Abstracts from the following conference proceedings were searched for the last three years (i.e. from 2012 to October 2015).

- American Society of Clinical Oncology (ASCO)
- International Melanoma Congress presented by the Society for Melanoma Research (SMR)
- European Society for Medical Oncology (ESMO)/European Cancer Organization (ECCO)
- International Society For Pharmacoeconomics and Outcomes Research (ISPOR)

Additional data reported in public assessment reports were searched from European Medicines Agency (EMA) and Food and Drug Administration (FDA) website. Further, Health Technology Assessment (HTA) guidance documents published in English were searched from NICE, Scottish Medicines Consortium (SMC), Pan-Canadian Oncology Drug Review (pCODR), Pharmaceutical Benefits Advisory Committee (PBAC), Institute for Quality and Efficiency in Health Care (IQWiG), and Agency for Healthcare Research and Quality (AHRQ).

Clinicaltrials.gov was searched to identify trials in progress that were investigating the interventions of interest. Table 73 presents inclusion and exclusion criteria for the systematic reviews of the economic and HRQL literature.

Table 73: Inclusion / exclusion criteria for the economic review

Eligibility criteria	Rationale
Inclusion criteria	
Population • Age: adults aged ≥18 years • Gender: any • Race: any • Disease: patients with BRAF V600 mutation positive metastatic malignant melanoma • Line of therapy: First or second line of therapy for the metastatic stage	• Mean age of diagnosis of melanoma is 50 years. Approximately 20% of cases of melanoma occur in young adults aged between 15 years and 39 years) • Melanoma can occur both in men and women, although the risk is higher in men than in women • Clinical trials and other studies usually enroll participants of all races. Focusing the inclusion on a particular race(s) would pose problems in conducting reviews and would limit the findings of the review to a particular race only. Moreover, the objective of the review does not restrict it to any particular race • Patient population was restricted to match the stated protocol for this review
Intervention and comparators • There were no restrictions on interventions or comparators in either review.	**Economic review:** • Interventions of interest for economic evaluations were similar to the clinical review and the review was restricted to studies of first- or second-line therapies (or those providing subgroup analyses of these lines). **Quality of life review:** • All treatments irrespective of the type were included in this review to collate all available published QoL related evidence in patients with MMM
Study design: **Economic review:** Evidence was not limited on the basis of study design. The key study designs to be included are listed below: • Cost studies/surveys/analyses • Database studies collecting cost data • Burden of illness • Resource surveys • Cost-effectiveness analyses • Cost-utility analyses • Cost-benefit analyses • Cost-minimization analyses • Budget impact models • Cost-consequence studies **Quality of life review:**	**Economic review:** • These study types were included in the review as they report an economic evaluation or provide data on cost of illness and economic burden **Quality of life review:** • These study types may collected and reported QoL/utilities data

• RCT • Non-randomised controlled clinical trials • Cohort studies/longitudinal studies (retrospective) • Cohort studies/longitudinal studies (prospective) • Case control studies • Cross sectional studies • Analysis of hospital records/databases • Single arm studies (uncontrolled trials)	
Countries • Any country	• All relevant studies irrespective of the location were included in this review to collate all available published economic and QoL related evidence in patients with MMM
Language restrictions: • English only	• Language restriction was not expected to limit results substantially and data was available in English language
Publication timeframe: • Database inception to 13 July 2015 for literature searches • 2012 to 2015 for conference searching	• Studies presented at conferences are usually published in journals within three years

Search strategies and inclusion/exclusion criteria for the economic review are provided in Appendix 8.11.

5.1.2. Description of identified studies

A full discussion of the results of the broad review, including the PRISMA diagram, is provided in Appendix 8.11. Retrieved studies were of limited relevance to this appraisal. Table 74 summarises the only cost-effectiveness analysis of trametinib in combination with dabrafenib that was identified and describes its limited relevance to this decision problem.

Table 74: Retrieved CEA of trametinib in combination with dabrafenib versus vemurafenib and DTIC

Reference Delea, T et al. 2014. [173]
Purpose of assessment In 2013 the manufacturer of trametinib and dabrafenib conducted a cost-effectiveness analysis in preparation for a previously scheduled NICE appraisal of this treatment.
Detail of economic evaluation A three state partitioned survival model (progression-free survival (PFS), post-progression survival (PPS) and death) projected the expected clinical and economic outcomes for previously untreated BRAFV600 mutation-positive metastatic melanoma patients assumed to receive treatment with either an intervention (dual therapy, dabrafenib monotherapy or trametinib monotherapy) or a comparator of interest (vemurafenib or dacarbazine). A 30-year time horizon was employed to represent the lifetime. Part C – a randomised phase of the phase II BRF113220 study which compared trametinib + dabrafenib versus dabrafenib monotherapy – was the basis for efficacy assumptions for the combination. The base case assumed no additional benefit of experimental treatment over control beyond the end of follow-up in the BRF113220 study (118 weeks for dual therapy and 73 weeks for monotherapies). Overall survival data from the BRF113220 study of dual therapy had been adjusted using RPSFTM for the confounding effects of treatment switching (80% of patients randomised to comparator had crossed over to the combination treatment arm following progression). PFS and OS for dacarbazine and vemurafenib were modelled as proportional hazards versus PFS and OS for dabrafenib monotherapy. Outcomes were measured in terms of quality adjusted life years (QALYs) based on individual residual life expectancy data and health related quality of life. The incremental cost components were BRAF testing, drug acquisition costs, drug administration costs, pre- and post-progression monitoring/ supportive care costs, costs of treating adverse events and the costs of post-study anti-cancer therapies.
Results of assessment The ICER for trametinib + dabrafenib combination versus vemurafenib in this assessment was £50,603/QALY. The ICER for trametinib + dabrafenib combination versus DTIC was £49,804. Incremental costs are confidential given the underlying confidential drug prices.
Applicability to this decision problem The study is of limited applicability in this assessment for the following reasons: • Price assumptions for the combination of trametinib and dabrafenib have subsequently changed • Clinical efficacy of the combination was less certain at the time and the assessment was based on the small phase II study BRF113220 study which was heavily confounded by treatment switching; in 2013, results from the COMBI-d and COMBI-v trials (phase III studies which underpin the assessment in this appraisal) were not yet available • The assessment makes no comparison of trametinib + dabrafenib combination versus

dabrafenib monotherapy.

5.1.3. QA of identified studies

A summary of the Drummond 10-point checklist as applied to the above analysis only is reproduced in Table 75 to Table 80 below.

Table 75: Summary of the quality assessment of included studies (in this appraisal) based on Drummond's checklist

Drummond's checklist for Economic evaluation studies										
Study Name	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Delea 2014	Y	Y	Y	NC	NC	NC	Y	NC	NC	NC

Table 76: Summary of critical appraisal of included studies (in this appraisal) based on Drummond's checklist (Q1-Q2.2)

Study name	Q1	Q1.1	Q1.2	Q1.3	Q2	Q2.1	Q2.2
Delea study UK	Yes; A well-defined question was posed in answerable form	Yes; The study examines both costs and effects of the service	Yes; The study involved comparison of alternatives	Yes; The viewpoint for the analysis was stated. The perspective considered was third party payer's perspective	Yes; the description of alternatives was described	No; There was no omission of relevent alternatives	No; Only Active interventions was compared

N: No; NC: Not Clear; Y: Yes; Q1: Was a well-defined question posed in answerable form?; Q1.1: Did the study examine both costs and effects of the service(s) or program(s)?; Q1.2: Did the study involve a comparison of alternatives?; Q1.3: Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?; Q2: Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?; Q2.1: Were there any important alternatives omitted?; Q2.2: Was (should) a do-nothing alternative be considered?

Table 77: Summary of critical appraisal of included studies (in this appraisal) based on Drummond's checklist (Q3-Q4.3)

Study name	**3**	**3.1**	**3.2**	**3.3**	**4**	**4.1**	**4.2**	**4.3**
Delea study UK	Yes; The effectiveness of the programme were established	Yes; Data from randomised controlled trials was used.	Yes; The effectiveness was established through an overview of clinical studies	Yes; Observational data or assumptions were used to establish effectiveness	Not clear; This was conference abstract and limited information was provided	Not clear; This was conference abstract and limited information was provided	Yes; The perspective was clearly stated	Not clear; This was conference abstract and limited information was provided

Q3: Was the effectiveness of the program or services established?; Q3.1: Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?; Q3.2: Was effectiveness established through an overview of clinical studies?; Q3.3: Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?; Q4: Were all the important and relevant costs and consequences for each alternative identified?; Q4.1: Was the range wide enough for the research question at hand?; Q4.2: Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.); Q4.3: Were the capital costs, as well as operating costs, included?

Table 78: Summary of critical appraisal of included studies (in this appraisal) based on Drummond's checklist (Q5-Q6.4)

Study name	Q5	Q5.1	Q5.2	Q6	Q6.1	Q6.2	Q6.3	Q6.4
Delea study UK	Not clear; This was conference abstract and limited information was provided	Not clear; This was conference abstract and limited information was provided	Not clear; This was conference abstract and limited informatio n was provided	Not clear; This was conference abstract and limited information was provided	Yes; The sources of all values were clearly identified	Yes; The costs were discounted at 3.5% per annum.	Not clear; This was conference abstract and limited informatio n was provided	Yes; Cost-utility method was used

Q5: Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?; Q5.1: Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?; Q5.2: Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?; Q6: Were the cost and consequences valued credibly?; Q6.1: Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgments); Q6.2: Were market values employed for changes involving resources gained or depleted?; Q6.3: Where market values were absent (e.g. volunteer labor), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?; Q6.4: Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?

Table 79: Summary of critical appraisal of included studies (in this appraisal) based on Drummond's checklist (Q7-Q9.3)

Study name	Q7	Q7.1	Q7.2	Q8	Q8.1	Q9	Q9.1	Q9.2	Q9.3
Delea study UK	Yes; Costs and consequ ences were adjusted for differenti al timing	Yes; The costs were discounted at 3.5% per annum.	Not clear; This was conference abstract and limited informatio n was provided	Not clear; This was conference abstract and limited informatio n was provided	Not clear; This was conference abstract and limited informatio n was provided	Not clear; This was conference abstract and limited informatio n was provided	Not clear; This was conference abstract and limited informatio n was provided	Yes; Sensitivit y analysis was employe d	Yes; The results were sensitive to change in values.

Q7: Were costs and consequences adjusted for differential timing?; Q7.1: Were costs and consequences that occur in the future 'discounted' to their present values?; Q7.2: Was there any justification given for the discount rate used?; Q8: Was an incremental analysis of costs and consequences of alternatives performed?; Q8.1: Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?; Q9: Was allowance made for uncertainty in the estimates of costs and consequences?; Q9.1: If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?; Q9.2: If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)?; Q9.3: Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

Table 80: Summary of critical appraisal of included studies (in this appraisal) based on Drummond's checklist (Q10-10.5)

Study name	Q10	Q10.1	Q10.2	Q10.3	Q10.4	Q10.5
Delea study UK	Not clear; This was conference abstract and limited information was provided	Not clear; This was conference abstract and limited information was provided	Not clear; This was conference abstract and limited information was provided	Not clear; This was conference abstract and limited information was provided	Not clear; This was conference abstract and limited information was provided	Not clear; This was conference abstract and limited information was provided

Q10: Did the presentation and discussion of study results include all issues of concern to users?; Q10.1: Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?; Q10.2: Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?; Q10.3: Did the study discuss the generalizability of the results to other settings and patient/client groups?; Q10.4: Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)?; Q10.5: Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' program given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programs?

5.2. De novo analysis

The objective of the economic evaluation was to assess the cost-effectiveness of trametinib in combination with dabrafenib (T+D) as a treatment for patients with BRAF V600 mutation positive unresectable or metastatic melanoma from the perspective of the NHS, versus both dabrafenib and vemurafenib monotherapies.

The phase III head-to-head studies comparing trametinib + dabrafenib combination versus vemurafenib (COMBI-v)[112] and versus dabrafenib (COMBI-d)[18] are deemed the most robust basis from which to answer these questions. These studies are described in detail in Section 4.3.

Fundamentally, the economic analysis is based on a one-stage meta-analysis of individual patient data from the two phase III trials, where data are pooled to estimate efficacy and safety parameters for economic modelling and where the impact of any heterogeneity between the studies is accounted for in the probabilistic sensitivity analysis.

The rationale for this approach is as follows:

- COMBI-d and COMBI-v studies are homogenous trials, as acknowledged by the EMA,[††] from both the perspective of their trial designs and their baseline patient characteristics (see Section 4.9 and Appendix 8.12). Each addresses the same fundamental research question if one accepts that dabrafenib and vemurafenib are interchangeable.
- Clinical evidence and clinical opinion[‡‡] consistently suggest that vemurafenib and dabrafenib have comparable efficacy. For the purpose of the economic analysis it is therefore reasonable to pool time to event data (i.e. individual patient level [IPD] OS and PFS data) from the comparator arms in the two trials.
- Individual patient level efficacy data from COMBI-v and COMBI-d were pooled by combining data on failure times (progression and death) and censoring for each participant into one dataset. As described in Section 5.2.2 below, the de novo model relies on area under the curve analyses for both PFS and OS applied independently to each arm to generate outputs. Kaplan-Meier curves were re-estimated from this pooled dataset for the combination arm and for BRAF inhibitor monotherapy, assuming - as detailed above - that dabrafenib and vemurafenib have comparable efficacy.
- Pooling significantly increases sample size and therefore the precision of the *area under the curve* (AUC) analyses that underpin the economic assessment. Whilst COMBI-v and COMBI-d are large, robust RCTs in their own right, they were powered to detect differences in OS and PFS hazard ratios only (respectively), and not for

[††] "The patient population included in the MEK115306 study and the MEK116513 study were comparable."
" The OS data for the combination therapy dabrafenib and trametinib obtained in studies MEK115306 and MEK116513 were comparable to each other."
[‡‡] "The Committee also heard from the clinical specialist that the clinical effectiveness of dabrafenib and vemurafenib were not considered to differ in clinical practice and that the choice between the 2 treatments would be largely based on their adverse reaction profiles"… "there was no clear evidence that dabrafenib and vemurafenib differed in clinical effectiveness and that it would not be unreasonable to assume that they have similar effect".

area under the curve or any other analyses. The additional precision that the pooling brings to estimates of the PFS and OS is important as past appraisals of treatments in this disease area consistently show that survival estimates are the key drivers of cost-effectiveness.

- In general, meta-analyses/pooling must account for underlying variability in the pooled datasets. KM estimations themselves do not typically adjust for stratification (whether within one trial or across trials in a pooled dataset) and there is no known way to do this in the break point analysis (See Section 5.3.1.2.) or in the combination of KM data and exponential curves. In this economic model therefore, the impact of inter-trial variability in the pooling of PFS and OS data is accounted for in the probabilistic sensitivity analysis. Here, PFS and OS are sampled from the two trials independently (i.e. with stratification by trial) during bootstrapping (see Section 5.8.2) ensuring the uncertainty that pooling introduces is accounted for.
- The comparability assumption for vemurafenib and dabrafenib does not hold for the safety profile or for pre-progression quality of life, again consistent with clinical opinion and evidence that the drugs have distinct adverse event (and therefore quality of life) profiles. These parameters are therefore incorporated separately for each BRAF inhibitor via an approach analogous to adjusted indirect treatment comparisons (where the monotherapies 'reference' the pooled combination data and randomisation is effectively maintained in the comparisons). The overall approach effectively allows for the incorporation of any priors regarding the relative effects of dabrafenib and vemurafenib (see Appendix 8.13).
- The proportional hazards assumption does not hold for these trials across PFS or OS (see Figure 29 and **Error! Reference source not found.**) and as such each arm in the dataset is treated independently. Summary statistics such as hazard ratios were not required for clinical reasons and are not applicable in the context of the economic model and, as described in Section 4.9, were not generated for the pooled dataset. Generating and using such summary data in economic modelling would imply that the proportional hazards assumption is reasonable and unless this is definitively shown, it has been criticised in several prior appraisals in this disease area. [81; 82; 83; 90]

The model is described in greater detail in the following sections.

5.2.1. Patient population

The economic evaluation includes patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. This is consistent with the patient group defined in the scope and decision problem for this appraisal and with the European marketing authorisation for the combination of trametinib with dabrafenib.

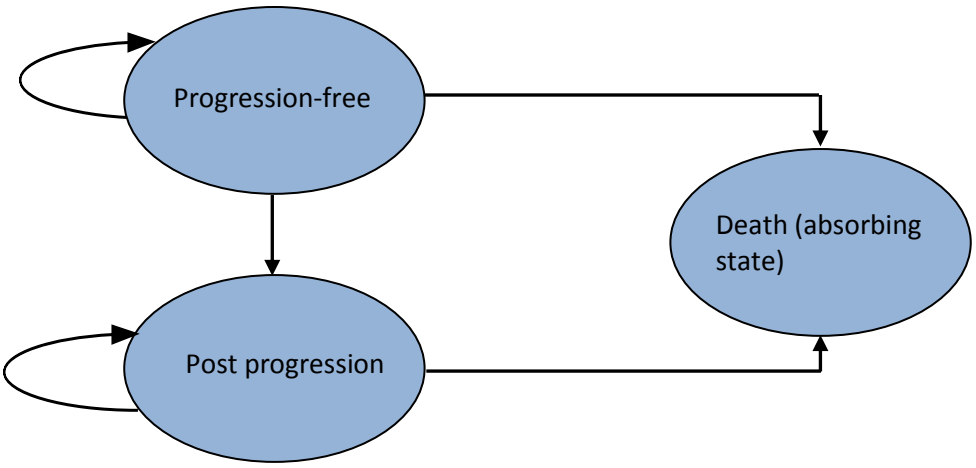
5.2.2. Model structure

A partitioned survival model was developed to determine the cost-effectiveness of trametinib in combination with dabrafenib. The structure of the model employed in this study is similar to that used in numerous prior economic assessments of treatments for advanced or metastatic

cancers. Patients were assumed to be in one of three mutually exclusive health states, reflected in Figure 28:

- Alive and no progression (PFS)
- Alive with progression (PPS); and
- Dead.

Figure 28: De novo model structure



The proportion of patients in each health state over time is estimated based on survival functions for progression-free survival (PFS) and overall survival (OS), themselves approximated through extrapolation of pooled individual patient time to event data from the most current empirical data from the pivotal studies (March 2015 datacut for COMBI-v and January 2015 for COMBI-d).

In the base case, an incremental analysis of combination versus vemurafenib and dabrafenib is presented. Costs and quality of life depend upon the treatment received and the expected time in the health states. For each therapy, expected PFS is calculated as the area under the curve for the PFS distribution. Expected OS is calculated as the AUC for the OS distribution. Expected PPS is calculated as the area between the PFS and OS curves or the difference between expected PFS and expected OS.

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

The modelled health states appropriately capture the patient journey through metastatic melanoma and the clinical pathway of care described in Section 3.3. Patients may experience changes in their quality of life corresponding to the progressive health states that are a feature of this disease. Disease progression is a key determinant of quality of life [174; 175] and of medical resource utilisation.

When therapy is initiated, patients who progress are assumed to be in the 'alive pre-progression' health state and are at risk of disease progression or death. Patients who progress are assumed to discontinue therapy and those who discontinue are assumed to transition to the 'alive and progressed' health state and to stay in that state until death.

The model has a cycle length of one week to permit consideration of therapies with different cycle durations (e.g. one, two, three and four weeks) and to eliminate the need for a half cycle correction.

Analyses were conducted from the perspective of the NHS and PSS in England. Accordingly, only direct medical costs were considered. The costs of trametinib, dabrafenib and vemurafenib are based on published list prices (as per the NICE requirement for this main submission document). Results of the analyses incorporating DH agreed confidential PASs (for dabrafenib and trametinib, and a range of potential discounts for vemurafenib) are presented in the PAS addendum.

Appendix 8.15 provides a technical description of how the model functions.

5.2.3. Features of the de novo analysis

The key features of the de novo analysis are summarised below in Table 81.

Table 81: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	30 years	30-year time horizon is a reasonable representation of the lifetime for patients in the model (mean age 55 years)
Were health effects measured in QALYs; if not, what was used?	Yes	As per reference case
Discount of 3.5% for utilities and costs	Yes	As per reference case
Perspective (NHS/PSS)	NHS	As per reference case
PSS, personal social services; QALYs, quality-adjusted life years		

Intervention technology and comparators

5.2.4. Implementation of interventions and comparators in the model

The intervention and comparators are implemented in the model as per their current marketing authorisations and doses, as described in Table 82 below.

Table 82: Characteristics of treatment regimens for therapies considered in the model

Drug	Type of Administration	Daily Dose (mg)	Basis of Daily Dose	Source
Dabrafenib (combination)	Oral	300	Per patient	Dabrafenib SPC
Trametinib (combination)	Oral	2	Per patient	Trametinib SPC
Dabrafenib	Oral	300	Per patient	Dabrafenib SPC
Vemurafenib	Oral	1920	Per patient	BNF

5.2.5. Treatment continuation / stopping rules

No clinical continuation or stopping rules have been implemented in the model. It is assumed that patients will be treated until their disease progresses, in line with the SPCs and the protocols in the underlying trials.

5.3. Clinical parameters and variables

5.3.1. Incorporation of the clinical data in the model

5.3.1.1. General features

PFS and OS during the trial period

As described in Section 5.2, survival modelling relies on pooled PFS and OS failure times from the latest data cuts from COMBI-v (March 2015) and COMBI-d (January 2015). Failure times for vemurafenib OS are from a patient level dataset which had been adjusted for treatment switching in the 6% of patients who were initially randomised to vemurafenib but whom switched to receive the trametinib-dabrafenib combination before the end of trial follow up (see Section 4.7). Kaplan-Meier PFS and OS survival curves were re-estimated for trametinib + dabrafenib combination and for BRAF inhibitor monotherapy from this pooled dataset (under the assumption that their efficacy is comparable); duration of follow up was defined as the maximum follow up in the pooled data.

PFS and OS beyond the trial period

Kaplan-Meier data were not complete in either study (therefore in the pooled dataset) and in order to estimate any long-term survival benefits associated with trametinib + dabrafenib combination, it was necessary to extrapolate PFS and OS beyond follow up. We concur with Bagust and Beale[176] that goodness of fit during the trial period may not be informative with respect to the accuracy of long-term projections, and long-term projections are highly sensitive to the specific parametric distribution employed. Therefore, the diagnostic steps taken to determine the most appropriate approach to extrapolation were consistent with those described by Bagust and Beale [176], in summary:

- An initial exploration of the possibility of parallel cumulative hazards after a shift in the cumulative hazard function; this approach is not pursued as there is no evidence that treatment arms in the pooled dataset exhibit parallel hazard functions (see Appendix 8.14)
- Use of independent survival distributions for treatment and comparator groups (rather than an assumption of proportional hazards which was not evident in the dataset)
- Use of Kaplan-Meier survival distributions for an initial period during the trial until evidence of long-term linear trends (following examination of the cumulative hazard function (-log KM estimated survival vs time))
- Assumption of constant hazard from the point at which the linear trend begins for the remainder of the projection, except if there is reason to believe there may be an

increase hazard of death due to age-related increase in mortality, or if there is a possibility of a cure.

On the basis of the above steps, the following approach was taken to modelling PFS and OS for the AUC analyses of each treatment arm in the base case analysis.

PFS:

- Use of Kaplan-Meier data for each treatment arm until a pre-determined break point beyond which a long-term linear trend was evident
- An assumption of constant hazards/exponential distribution applied to each arm separately in the projection period, therefore:
- An implicit assumption that the observed PFS benefit associated with trametinib in combination with dabrafenib would continue beyond trial follow up.

OS:

- Use of Kaplan-Meier data for each treatment arm until a pre-determined break point beyond which a long-term linear trend in hazards was observed
- An assumption of constant hazards from the break point until year 5 when it is assumed that mortality rates would converge with those from the AJCC Melanoma Registry (case-mix adjusted)
- Use of age- and gender-matched general population mortality rates beyond 20 years, accounting for the relatively increased risk of death in the metastatic melanoma population versus the general population (i.e. preserving the residual increased mortality and not assuming cure).

5.3.1.2. Approach to break-point analysis to establish long-term trends

There is no published recommended approach to determining that point in time which represents a changing pattern in the hazard function. In critiques of several past NICE appraisals in metastatic melanoma, [81,82] the approach has tended to rely on a visual inspection of the cumulative hazard plots of the PFS and OS survival functions.

In this analysis, break points in the pattern of PFS and OS hazards beyond which a linear trend was evident were determined as follows: cumulative hazards are plotted at each failure point with at least 10 patients at risk (failure points with less than 10 patients at risk were not likely to provide robust fits and were discarded). At each break point, a piecewise linear curve was fit to the cumulative hazards in R using the piecewise.linear function from the “SiZer” package. The piecewise.linear function uses a general purpose optimiser to solve for the likelihood-maximising breakpoint. The fitted piecewise linear model on the cumulative hazards is equivalent to a piecewise exponential distribution. This approach was deemed more robust than using a visual inspection of the curves to approximate a change in hazard trends.

5.3.1.3. Progression free survival

Plots showing the piecewise linear fits to the cumulative hazards used to identify the break points for PFS for the combination and BRAFi monotherapy (under the assumption that vemurafenib and dabrafenib have comparable efficacy) are shown in Figure 29 below. Steeper slopes imply higher rates of hazard. The points denote the cumulative hazard at failure times, whereas the lines show the piecewise linear regression model. A vertical line is drawn at the time of the break point for each arm of the dataset.

Figure 29 [redacted]

The hazards based on the break points for trametinib + dabrafenib combination and BRAF inhibitor monotherapy are provided in Table 83.

Table 83: Break points and exponential hazards after the break points for PFS for trametinib + dabrafenib and BRAF inhibitor monotherapy in COMBI-v and COMBI-d combined

Treatment	Cut-Point (Months)				Hazard Rate (Monthly)			
	Estimate	SE	95%CI L	95%CI U	Estimate	SE	95%CI L	95%CI U
T+D	11.8	1.4	9.7	14.5	0.0360	0.0046	0.0268	0.0451
BRAF Inhibitor	12.5	1.3	9.7	14.5	0.0519	0.0082	0.0373	0.0685

The PFS projections for trametinib + dabrafenib and BRAFi monotherapy obtained by combining the Kaplan Meier curve and the constant hazards derived from the breakpoint analysis above are shown in Figure 30.

Figure 30: [redacted]

By applying constant hazards independently to each arm, the long-term projections for PFS assume that the PFS benefit apparent during the trial period for trametinib + dabrafenib combination continues beyond trial follow up. The assumption is explored in a scenario analysis.

Long-term projections of PFS for trametinib + dabrafenib combination and BRAF inhibitor monotherapy obtained by combining the Kaplan Meier curve and constant hazards derived from the break point analysis are shown in **Error! Reference source not found.**.

Figure 31: [redacted]

5.3.1.4. Overall survival

As with PFS, piecewise linear fits to cumulative hazards were used to identify changes in the hazard trend for OS for the combination and monotherapy. These are shown in **Error! Reference source not found.**. A vertical line is drawn at the time of the break point for each of the trial arms.

Figure 32: [redacted]

The hazards based on the break point for trametinib + dabrafenib combination and BRAFi monotherapy are provided in Table 84. The break points are approximately 19 months for the combination and 3 months for monotherapy.

Table 84. Break points and exponential hazards after the break points for OS for trametinib + dabrafenib and BRAF inhibitor monotherapy

	Cut-Point (Months)				Hazard Rate (Monthly)			
Treatment	**Estimate**	**SE**	**95%CI L**	**95%CI U**	**Estimate**	**SE**	**95%CI L**	**95%CI U**
Dabrafenib-Trametinib	18.6	4.2	4.2	21.0	0.0228	0.0050	0.0150	0.0348
BRAF Inhibitor	3.2	6.3	2.8	23.3	0.0441	0.0121	0.0300	0.0704

The monthly hazard rate at the time of the break point was then assumed to apply beyond this time. Figure 31 demonstrates that the exponential segments fit the Kaplan Meier distributions reasonably well, and are within the 95%CIs for the Kaplan Meier distributions throughout the trial period, with the exception of the projection for BRAF inhibitor monotherapy at approximately 32 months.

Figure 31: [redacted]

Figure 32 however shows that applying the monthly hazards from the break point analysis for the duration of the lifetime results in projections with limited face validity in light of known/observed long-term overall survival data for patients with metastatic melanoma.

Figure 32 [redacted]

The figure above shows that OS for the monotherapy arm is projected to be 0% before 10 years whilst for the combination therapy the projection predicts 0% survival by approximately 15 years. These results are inconsistent with OS data from the AJCC melanoma registry, SEER data, and long-term follow up of the DTIC arm of the CA184-024 trial, all of which suggest that the annual probability of death in patients with metastatic melanoma declines from approximately 60% in year one to 10%-15% at 5 years, and to 5%-10% between 5 and 10 years (see Appendix 8.16 for a full discussion of the literature on long-term survival in this patient group).

As reported in Table 84 above, the monthly hazards for OS for combination and BRAF inhibitor monotherapy based on the break point analysis were estimated to be 0.023 and 0.044, respectively, which correspond to annual hazard rates of 0.276 and 0.528 and therefore probabilities of mortality of approximately 0.24 and 0.41, respectively[h]. These predicted mortality probabilities are considerably higher than the long-term annual mortality probabilities described above. We therefore conclude that long-term projections based solely on exponential decay/constant hazards assumption substantially underestimates survival in the longer term in both treatment arms.

Accordingly, the OS Kaplan-Meier curves and the exponential extrapolation were combined with long-term survival data from the AJCC melanoma registry. Consistent with patterns of survival from long-term data (suggesting a rapid drop in survival initially and a plateau from approximately 5 years), it was assumed that mortality rates during the projection period would converge with case-mix adjusted estimates of mortality from the AJCC Melanoma Registry from year 5.

[h] Combination therapy: annual probability = 1-exp(-annual rate) = 1-exp(-0.276) =0.24
BRAF inhibitor monotherapy: annual probability = 1-exp(-annual rate) = 1-exp(-0.528)=0.41

AJCC Melanoma Registry data represent a large sample of (relatively) geographically-diverse patients with metastatic melanoma and provide the longest duration of follow-up among the various sources of long-term data. Additionally, mortality data are available in subgroups according to whether disease has metastasised or not; it was therefore possible to calculate case-mix adjusted estimates of survival for trametinib + dabrafenib combination, dabrafenib and vemurafenib using the AJCC data and the distribution of patients by 'M stage' in the dataset.[i] The method for case-mix adjustment of AJCC for the pooled dataset is presented below in Box 1. It relies on the use of digitized curves and the method described by Guyot and colleagues.[177]

Box 1: Method for case-mix adjustment of OS for pooled data-set

Kaplan-Meier survival curves for stage IIIc and stage IV melanoma were digitised. Approximate patient level survival data for each stage were generated using the digitised curves and methods described by Guuyot and colleagues. Using these data a variety of parametric distributions were fit to the survival data for each M stage including the exponential, Weibull, log-logistic, lognormal, Gompertz, generalized F, generalized Gamma, RCS odds, RCS hazards, and RCS normal models. The goodness of fit of these parametric distributions were assessed by visual inspection and AICc statistics. Based on AICc, the RCS models provided the best fit across all stages.

As shown below the RCS models all fit the survival curves well (indicated by the overlap of parametric extrapolations and the raw data for each stage in the figure below). The RCS normal distribution was used for all stages because it provided the best fit overall.

Figure 33: [redacted]

Case-mix adjusted survival curves were then calculated for each arm in the pooled dataset by weighting the stage-specific RCS normal curves by the proportion of patients within each stage (stages in pooled dataset shown below).

[i] We acknowledge that a criticism has been levelled previously against using case-mix adjusted AJCC survival trends directly to inform survival projections (ipilimumab second line submission), however this was in a second-line advanced melanoma patient population in which it is reasonable to assume that the case-mix may have changed in the period between diagnosis and second-line treatment. This is unlikely to be relevant in the context of frontline treatments where patients will be treated relatively soon after diagnosis.

M Stage	Pooled data					
	T+D		Mono		Total	
	N	(%)	N	(%)	N	(%)
M0	19	(3)	10	(5)	15	(4)
M1a	74	(13)	31	(15)	50	(12)
M1b	106	(19)	32	(15)	77	(18)
M1c*	363	(65)	138	(65)	280	(66)
Total	562	(100)	211	(100)	422	(100)

*includes unknown

Survival based on AJCC melanoma registry data adjusted to the M stage distribution in the pooled dataset is shown in **Error! Reference source not found.** below.

Figure 34 [redacted]

Outcomes and costs after 20 years are projected using age- and gender-matched general-population mortality rates, which are scaled up proportionally to account for the increased relative risk of mortality in this population (i.e. there is no assumption that patients are 'cured' in this model consistent with literature suggesting ongoing residual elevated risk of death in patients with metastatic melanoma, see Appendix 8.16).[j]

Figure 35 below shows the survival distributions when OS data are based on the Kaplan-Meier curves (to the predetermined break point) followed by an assumption of constant

[j] This is achieved in the model by applying the risk ratio for [annual death rate at 20 years in model: annual general population mortality at 75 years] to the probability of death for patients entering the life table calculation

hazards thereafter until converging with case-mix adjusted AJCC survival trends from 5-20 years and then adjusted general population mortality data.

Figure 35 [redacted]

[redacted]

5.3.1.5. Adverse events

Adverse events are incorporated separately for the trametinib + dabrafenib combination, dabrafenib and vemurafenib into the model to ensure that incremental costs have accounted for the differing safety profiles of the individual treatments. The costs of AEs are incorporated as described in Section 5.5.7.

Any decrements in quality of life that may be associated with particular adverse events are implicitly captured in the model given the approach taken here to valuing the health states (namely using utility data directly from the underlying phase III trials; see Section 5.4).

5.3.2. Transition probabilities

Transition probabilities are not estimated in a partitioned survival analysis. The proportions of patients in each treatment group who reside in each health state over time are derived from the PFS and OS survival functions. An area under the curve analysis is used to estimate mean progression-free and overall survival. The difference between these two curves provides an estimate of the mean time alive following disease progression.

5.3.3. Transition probabilities over time

See above.

5.3.4. Assessment or approximation of clinical parameters by clinical experts

Clinical parameters in the model were derived directly from the underlying phase III trials COMBI-v and COMBI-d and it was not necessary to rely on clinical experts for approximation or estimation of these data.

5.4. Measurement and valuation of health effects

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

Method of elicitation

Section 4 describes the assessment of health-related quality-of-life (HRQL) in both COMBI-v and COMBI-d trials in great detail. Table 85 summarises the key details of these analyses that are relevant to the economic modelling, namely the EQ-5D assessments. EQ-5D is a measure of utility that generates an index-based summary score based on societal preference weights. The NICE reference case prefers the generic EQ-5D in adults as reported by the patient, using the value set obtained from a representative sample of the UK general population using time-trade off. This is the approach taken in this assessment.

Table 85: Collection of EQ-5D in COMBI-v and COMBI-d

	COMBI-v (April 2014)	COMBI-d (August 2013)
Method of elicitation	EQ-5D	EQ-5D
Method of valuation	Pre-existing value set for 3L (based on TTO with UK general population)	Pre-existing value set for 3L (based on TTO with UK general population)
Point when measurements were made	Baseline, week 8 and every 8 weeks thereafter through to week 56 and then every 12 weeks until disease progression. Assessments were also performed at the time of disease progression and 5 weeks post-progression.	Baseline, week 8 and every 8 weeks thereafter through to week 56 and then every 12 weeks until disease progression. Assessments were also performed at the time of disease progression and 5 weeks post-progression.
Consistency with reference case	Consistent	Consistent
Appropriateness for cost-effectiveness analysis	Preferred	Preferred
Results with confidence intervals	See below, Section 5.4.12	See below, Section 5.4.12

5.4.2. Mapping

Mapping was not required to estimate health state utility values as EQ-5D data were derived directly from the underlying phase III trials.

Health-related quality-of-life studies

5.4.3. Literature search

A systematic review was conducted to identify literature assessing the humanistic burden among patients receiving treatment for metastatic melanoma. This was a comprehensive systematic review across all first- and second-line treatments for metastatic melanoma.

Sources of literature, search strategies and inclusion/exclusion criteria for the HRQL review are provided in Appendix 8.11.

5.4.4. HRQL studies

Only two studies identified by the literature review were directly relevant to the economic modelling for this decision problem – the randomised controlled trials of the trametinib + dabrafenib, COMBI-v and COMBI-d. The methods and results of the quality of life analyses in these trials are described in detail in Section 4.7.1.3.

5.4.5. Comparison with clinical trial results

N/A – the relevant studies identified in the HRQL literature review are the pivotal trials for the trametinib + dabrafenib combination.

Adverse reactions

5.4.6. Adverse reactions and HRQL

The impact of trametinib + dabrafenib combination therapy on quality of life is reflected in the findings of the COMBI-d and COMBI-v trials and is discussed in detail in Section 4.7.1.3 and Section 4.7.2.3. Assessments in the trials were not undertaken in such a way that any impact on quality of life could be directly associated with a particular adverse event. Overall, the HRQL analyses in these trials demonstrate statistical and clinically meaningful improvements in many aspects of quality of life over vemurafenib and dabrafenib monotherapy, confirming that the potential exposure to more adverse events through receiving the two drugs does not negatively impact on HRQL.

In the economic model, the health states are valued using utility data derived directly from the COMBI-v and COMBI-d trials and as such they indirectly account for the impact of adverse events associated with the intervention and comparators.

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

5.4.7. Patient experience in the defined health states

Several studies have attempted to quantify the impact of different stages of melanoma on HRQL (Cornish, 2009; Gibbons, 2013, Cormier, 2012). Distress is common at the time of diagnosis and following treatment)[64]. Patients with advanced melanoma experienced high levels of psychologic distress, which affected their overall HRQL.[178].Cancer-specific HRQL instruments such as the FACT-G and FACT-M questionnaires have confirmed that patients with advanced disease have a poorer HRQL than patients with early-stage melanoma. [63; 70]

During treatment, poor quality of life scores can be linked to the adverse events associated with therapy. [179; 71] As described below, the models here use treatment specific utility data directly from the COMBI-v and COMBI-d trials to value the pre-progression health state. Decrements in HRQL associated with treatment-related adverse events are therefore incorporated.

Anxiety is common in the post-treatment follow-up stage[180] and patients may have considerable psychological needs[181; 4] relating to fear of cancer progression, [181; 181] uncertainty about the future and lack of information. [181]

5.4.8. Constancy of HRQL in the cost-effectiveness analysis

HRQL is impacted by total time in PFS and PPS health states. Within each health state it is assumed that quality of life is constant over time, i.e. a single utility applies to that health state. This is not an uncommon approach to modelling, however literature suggests that the assumption of constant utility in the post-progression state may not capture the decline in HRQL in the final months of life of advanced melanoma patients. In this case, post-

progression quality of life data were collected at progression and 5 weeks after disease progression so it was not possible to account for the association between utilities and time to death (see Section 5.4.11).

5.4.9. HRQL at baseline

Baseline EQ-5D assessments are not used in the cost-effectiveness modelling. In both COMBI-v and COMBI-d, mean EQ-5D utility values at baseline were comparable between the two treatment arms (0.751 vs. 0.715 for vemurafenib monotherapy and 0.765 vs. 0.730 for dabrafenib monotherapy, respectively).

5.4.10. Adjustment to health state utility values in the CEA

The assumption of comparable efficacy for the BRAF-inhibitors does not extend to adverse events or to quality of life. Accordingly, because there are no randomised controlled trials which simultaneously compared trametinib + dabrafenib with dabrafenib monotherapy and vemurafenib monotherapy, it was necessary to estimate utility values for each of the BRAF inhibitors using what amounts to indirect treatment comparisons.

- Utility values for the progression-free health state for trametinib + dabrafenib combination were based on the weighted average of all pre-progression utility assessments (excluding baseline) for this treatment in the pooled EQ-5D data (April 2014 cut off for COMBI-v and August 2013 cut off for COMBI-d). These were the latest datacuts available for this endpoint at the time of modelling (see Section 4.7.1.3 and Section 4.7.2.3).
- The progression-free health state utility value for vemurafenib was estimated by combining the PFS utility for trametinib + dabrafenib (estimated above) with the difference in the estimated PFS utility value for vemurafenib vs. trametinib + dabrafenib in COMBI-v (0.7502 - 0.8409= -0.0908).
- The progression-free health state utility value for dabrafenib monotherapy was estimated by combining the PFS utility for trametinib + dabrafenib (estimated above) with the difference in the estimated PFS utility value for dabrafenib vs.trametinib + dabrafenib in COMBI-d (0.7792 - 0.8270= -0.0479).
- The utility value for PPS was assumed to be the same across all treatments and was obtained by pooling the average of all post-progression assessments from COMBI-d (0.6998), and COMBI-v (0.6953) using random effects meta-analysis.

Section 5.4.12 summarises the utilities that were implemented in the model.

5.4.11. Health effects not included in the CEA

Literature suggests that the progression-based approach for modelling HRQL where there is no accounting for the time to death may underestimate the average utility value in the post-

progression health state.[42] This is because it assumes a constant utility and isn't sensitive to any changes in quality of life which may occur after progression. Quality of life during the post-progression health state is likely to be impacted by a number of factors (see Section 5.4.7) and has been shown to be associated with time to death in metastatic melanoma patients [42]. In both COMBI-v and COMBI-d, EQ-5D assessments were measured shortly after progression (5 weeks), and because they were not collected routinely until death in either study, an alternative approach – which may have allowed the model to account for changes in quality of life in the PPS health state – was not possible.

Secondly, BRAF inhibitors can have a rapid effect on tumours. The principle outlined above applies in the pre-progression state too and the approach used to model HRQL is not sensitive to the potentially differing impact that time from treatment initiation may have on quality of life. It is unclear in what direction and to what degree these two factors would affect the CEA presented here.

5.4.12. Summary of utility values used in the CEA

EQ-5D assessments were collected at screening, week 8, and then every 8 weeks thereafter through to week 56, and then every 12 weeks until disease progression in both studies. Assessments were also performed at the time of disease progression and 5 weeks post-progression.

Section 5.4.10 describes how EQ-5D utilities were used to value the pre- and post-progression health states for each treatment in the model. Table 86 presents the actual utility values implemented. The utilities are consistent with those derived from other phase III studies in this disease area.[81]

Table 86: 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 dabrafenib-trametinib (0.8369) and difference in weighted average of all pre-progression utilities assessments (excluding baseline) for vemurafenib vs. dabrafenib trametinib in COMBI-v (-0.0908).COMBI-v
Dabrafenib	0.789	0.011	Calculated based on estimated utility for dabrafenib-trametinib (0.8369) and difference in weighted average of all pre-progression utilities assessments (excluding baseline) for dabrafenib vs. dabrafenib 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.

5.4.13. Validation of HSUV data

The trial data were deemed the most appropriate source of utility values for this economic model and we did not seek to estimate them from alternative sources nor validate them externally.

5.5. Cost and healthcare resource use identification, measurement and valuation

5.5.1. Parameters used to estimate cost effectiveness

A summary of all variables used in the cost-effectiveness analysis is presented in Table 98 in Section 5.6.1 below.

Resource identification, measurement and valuation studies

5.5.2. Identification of cost and healthcare resource use data

As described in Section 5.1.1, a systematic literature review was conducted to identify economic studies, including cost-effectiveness analyses and studies reporting healthcare resource and costs associated with the treatment of advanced melanoma patients.

The methods of this review have been previously described and the detail is presented in Appendix 8.11.

A total of eleven studies in this review reported costs and resource use data, none of which were conducted in the UK. As such these studies are not deemed relevant to this decision problem and are not discussed further. The systematic review excluded studies which did not provide a 'subgroup analysis' or a discussion of patients receiving first- or second-line treatments. As such it did not include publications of the UK MELODY study.

In spite of this and acknowledging the fact that this study pre-dates the availability of newer treatments for metastatic melanoma (including the BRAF inhibitors and ipilimumab), MELODY is still considered the most reliable reflection of UK clinical practice in melanoma treatment and has been utilised in several recent NICE submissions.[81; 89; 83; 90; 82] It is therefore the basis for costing additional resource use in the pre- and post-progression health states, as described in detail in Section 5.1.1.

5.5.3. Current costing in NHS terms

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

5.5.4. Validation of healthcare resource use data

Resource use data are taken from the Oxford Outcomes MELODY study detailed in the ipilimumab, dabrafenib and pembrolizumab NICE submissions.[81; 89; 90] MELODY is a resource use survey with six UK clinical experts experienced in treating advanced melanoma patients. Additional validation of these published data was not deemed necessary given their original source.

Intervention and comparators' costs and resource use

5.5.5. Costs and associated healthcare resource for each treatment

Discounting is applied to all costs on an annual basis beginning at the end of the first year of the model.

BRAF screening costs

The cost of screening for BRAF mutation is not included in this economic model. This exclusion makes no material difference to the conclusions as the cost of testing would apply equally to intervention and comparators. The availability of targeted agents means it is emerging standard practice to test patients for this mutation when they are diagnosed.

Technology acquisition costs

Unit costs of medications

Treatment and comparators are implemented in the model as per their current marketing authorisations, see Table 82. Medication cost per day was calculated as the product of unit cost (per mg) and dosage (in mg) per day. The cost per mg for each drug was obtained by dividing the cost per unit (e.g., tablet or vial) by the mgs per unit. Prices of dabrafenib and vemurafenib were based on list prices from the BNF.

Table 87. List prices of dabrafenib and trametinib and vemurafenib

Drug	Package Size	List Price		
		Package Price (£)	Tab Price (£)	Mg Price (£)
Trametinib 2mg tablet	30	4,800	160.00	80.00
Dabrafenib 75mg capsule	28	1,400	50.00	0.67
Vemurafenib 240 mg tablet	56	1,750	31.25	0.13

The costs of study medications per 28 day cycle at list prices are presented in Table 88.

Table 88. Costs of study medications (list prices, not accounting for PAS)

Regimen	Drug	Unit Price	Mg per Unit	Price per mg (£)	Cost per Dose (£)	Cost per 28 Days (£)*
Trametinib + dabrafenib combination	Dabrafenib	£50.00 per capsule	75	0.67	200.00	5,600.00
	Trametinib	£160.00 per tablet	2	80.00	160.00	4,480.00
Dabrafenib monotherapy	Dabrafenib	£50.00 per capsule	75	0.67	200.00	5,600.00

Vemurafenib monotherapy	Vemurafenib	£31.25 per tablet	240	0.13	250.00	7,000.00

Relative Dose Intensity (RDI)

The model calculates the amount of medication and number of administrations of medication received based on the planned dose of the medication and the distribution of PFS, assuming patients are treated until progression. However, the actual amount of medication and number of administrations may be different due to dose reductions, treatment interruptions, and differences between the distribution of time to discontinuation and the distribution of PFS. To scale for the impact that this would have on treatment costs, the model includes relative dose intensities (RDIs) for medication costs and for administration costs. RDIs are an estimate of the ratio of estimated actual cumulative dose (in mg) to the estimated planned cumulative dose.[‡‡‡]

Actual and planned cumulative doses for the combination were derived from the pooled combination data across COMBI-d and COMBI-v. RDIs for dabrafenib monotherapy and vemurafenib are incorporated via what amounts to an ITC:

- For vemurafenib monotherapy, RDIs were obtained by multiplying the RDIs for trametinib-dabrafenib combination from the pooled dataset by the ratio of the RDI for vemurafenib versus trametinib-dabrafenib combination from COMBI-v. Here, estimates were based on data on exposure, time on treatment, and PFS from the April 2014 data cut in COMBI-v, prior to the IDM allowing treatment switching in this study. This approach is consistent with the use of RPSFTM adjusted OS from the trial.

- For dabrafenib monotherapy, RDIs were obtained by multiplying the RDIs for trametinib-dabrafenib combination from the pooled dataset by the ratio of the RDI for dabrafenib monotherapy versus trametinib-dabrafenib combination from COMBI-d (Jan 2015 datacut).

[‡‡‡] Actual and planned cumulative doses were estimated using the Kaplan-Meier sample average (KMSA) method. The actual cumulative dose was calculated as the sum over all study days of the product of the probability of being alive and on therapy each day and the mean dose among patients who were alive and on therapy on each day. The planned cumulative dose was similarly calculated as the sum over all study days as the product of the probability of being alive and progression-free on each day and the planned dose on each day. The actual and planned number of days on therapy was calculated similarly. The actual number of days on therapy was calculated as the sum over all study days of the product of the probability of being alive and on treatment each day and the proportion of patients who were alive and on treatment and had a non-zero dose on each day. The planned number of days on therapy was calculated as the sum over all study days of the proportion of patients alive and progression-free on each day. Investigator-assessed PFS was used in the calculation of RDIs.

Table 89: Estimated RDIs for intervention and comparators in base case

Therapy	RDI		Source
	Medi-cation	Admin-istration	
Trametinib + dabrafenib			
Dabrafenib	0.92	1.01	Analysis based on trametinib + dabrafenib combination data from pooled dataset.
Trametinib	0.96	1.00	
Vemurafenib monotherapy	0.84	0.96	Ratio of the RDIs for vemurafenib monotherapy vs. combination in COMBI-v multiplied by the RDI for the combination (estimated above)
Dabrafenib monotherapy	0.93	0.99	Ratio of the RDIs for dabrafenib monotherapy vs. combination in COMBI-d multiplied by the RDI for the combination (estimated above)

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

Wastage

The model assumes that patients receiving trametinib + dabrafenib combination, dabrafenib monotherapy and vemurafenib will receive a 28-day supply of medicine with each prescription and that any unused medication for patients who discontinue treatment during a cycle will be discarded.

Body Surface Area and Weight

Mean BSA and weight are used in the estimate of PSACT costs (not for the intervention and comparators). They were calculated using IPD from the BREAK-3 trial. For each patient, BSA was calculated from height and weight using a widely used formula devised by Du Bois and Du Bois: weight (kg) 0.4256 × height (cm) 0.7256 × 0.007184 (120).[§§§] The estimated mean BSA and weight are shown in Table 90.

Table 90. Estimated mean BSA and weight from BREAK-3

Parameter	Mean
BSA, m^2	1.93
Weight, kg	80.13

[§§§] The Du Bois and Du Bois formula was derived based on the measurement of two-dimensional surface area of plaster of Paris moulds of nine subjects. The age, sex and nutrition of these subjects, studied in the middle of the First World War, are unlikely to be comparable to that of cancer patients today. Several other formulas have since been proposed but none of those has gained widespread acceptance.

Dispensing and administration costs

A dispensing cost of £13.60 is assumed to be associated with each prescription. This is based on the cost of 12 minutes of hospital pharmacists time (hourly rate of a hospital pharmacist £68.00÷5=£13.60). Trametinib + dabrafenib combination, dabrafenib and vemurafenib were assumed to be prescribed every 4 weeks (28 days).

5.5.6. Health-state unit costs and resource use

Alongside costs associated with treatment acquisition and dispensing (outlined above), the model includes other monthly state-specific as well as one-off costs for initiation of therapy and death.

The monthly costs of melanoma-related care pre- and post-progression were assumed to include routine follow-up visits, lab tests and scans. Resource use was derived from the MELODY study, updated with 2013/2014 NHS reference costs.

Table 91 summarises the one-off costs associated with treatment in the economic model.

Table 91: One-off costs associated with treatment in the economic model

Other cost	Value, £	Reference
Treatment initiation (one-time)	£400	Ipilimumab submission to NICE[89]
Terminal care	£7,287	Georghiou and Bardsley (2014)[182]

Monthly costs are summarised in Table 92 below and detailed in Appendix 8.17.

Table 92: Health states and associated monthly costs in the economic model (costs are rounded for simplicity)

Health State	Service	Cost, £	Reference
PFS	Outpatient visit (GP and plastic surgeon)	6	NHS Ref Costs 2013-2014 (resource use from NICE ipilimumab submission) (reference)
	Inpatient stay	35	
	Laboratory tests	7	
	Radiological exams	100	
	Total	**148**	
PPS	Outpatient visit (largely medical oncologist)	247	NHS Ref Costs 2013-2014 (resource use from NICE ipilimumab submission) (reference)
	Inpatient stay	35	
	Laboratory tests	7	
	Radiological exams	101	
	Total	**390**	

*any discrepancies are due to rounding

5.5.7. Adverse reaction unit costs and resource use

Cost of treatment of adverse events

The model only incorporates the costs of treating those adverse events which are likely to have the greatest impact on NHS resource. This short list was derived by selected Grade 3+ AEs with an incidence of ≥5% in either arm of COMBI-v (March 2015 datacut) or COMBI-d (January 2015 datacut).

Table 93 reports these AEs along with their incidence.

Table 93: Incidence of G3/4 AEs >= 5% in any arm

Grade 3+ Adverse Event	COMBI-V		COMBI-D	
	T+D	Vemurafenib	T+D	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%

*combines SCC and SCC of the skin in estimation

Model inputs for trametinib + dabrafenib were estimated by a weighted pooling of the incidences in the combination arm across the trials. The incidence of AEs for vemurafenib and for dabrafenib monotherapy were estimated via indirect treatment comparisons:

- For vemurafenib: The incidence of G3+ AEs is estimated by applying the relative risk of each event from COMBI-v to the incidence of that event for combination from the pooled dataset.
- For dabrafenib: The incidence of G3+ AEs is estimated by applying the relative risk of each event from COMBI-d to the incidence of that for combination from the pooled dataset.

The pooled incidence of G3+ AEs with combination and the relative risks of these AE's with monotherapies are described in Table 94.

Table 94: Relative risks of the various G3+ AEs for the monotherapies

	Trametinib + dabrafenib combination	RR vs. trametinib + dabrafenib combination	
Adverse event	**COMBI-d and COMBI-v (N=559)**	**Vemurafenib**	**Dabrafenib**
Hypertension	11.81%	0.61	1.07
Rash	0.54%	10.03	10.03
Squamous cell carcinoma	1.79%	10.43	10.43
Keratoacanthoma	0.54%	17.55	17.55
Pyrexia	5.55%	0.13	0.13
Basal cell carcinoma	2.15%	0.50	0.50

The costs of treating AEs were calculated by multiplying the incidence of treatment-related AEs by the expected cost of these events.

- Estimates of the cost of treating Grade 3+ rash and Grade 3+ SCC were based on a cost-of–illness study performed by INC Research (updated to 2013-2014 NHS reference costs), which assessed the medical resource costs of treating and managing AEs associated with treatment for metastatic melanoma in the UK.[183]
- Grade 3 or higher keratoacanthoma and basal cell carcinoma were assumed to have the same cost as Grade 3 or higher SCC.
- The costs of treating Grade 3+ pyrexia and hypertension were assumed to include an outpatient visit to a medical oncologist (Currency Code 370-Consultant Led: Follow Up Attendance Non-Admitted Face to Face, NHS Ref Costs 2013-14, NHS Trusts and NHS Foundation Trusts, £143).
- All cases of pyrexia and one-half of hypertension cases were assumed to be hospitalised; calculation of inpatient costs for patients hospitalized with hypertension are shown in Appendix 8.18;

The estimated costs of adverse events assumed in the economic model for each event are shown in Table 95.

Table 95: 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 critieria of ≥5% incidence in either treatment arm of COMBI-V or COMBI-D.
†SE assumed to be 50% of base case value

5.5.8. Miscellaneous unit costs and resource use

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

Expected PSACT costs per patient were estimated as a weighted sum of the expected total PSACT cost per patient progressing in each trial. PSACT costs per trial were the sum of the product of the mean utilisation and the cost of a single course of the treatment (including administration costs). Mean utilisation for trametinib + dabrafenib combination was obtained by pooling data for patients receiving the combination from COMBI-v and COMBI-d (weighted for trial size). For dabrafenib and vemurafenib monotherapy PSACT costs were estimated via what amounts to an indirect treatment comparison:

- Utilisation of various PSACTs among patients receiving vemurafenib was obtained by combining these values with the differences between vemurafenib monotherapy and combination in COMBI-v.
- Utilisation of various PSACTs among patients receiving dabrafenib was obtained by combining these values with the differences between dabrafenib monotherapy and combination in COMBI-d.

The utilisation of PSACT in the pooled dataset and the characteristics and costs of the individual regimens are reported in further detail in Appendix 8.19. The expected costs of PSACT per patient over the lifetime using this methodology are reported in **Table 96**.

Table 96: Expected mean PSACT cost per patient in base case model*

Therapy	Cost per Patient, £	
	Mean	SE
Trametinib + dabrafenib combination	£55,220	£13,805
Vemurafenib	£65,002	£16,251
Dabrafenib	£69,617	£17,404

* PSACT estimates were adjusted for censoring given that patients who do not progress are not at risk of receiving PSACT.

Table 97 summarises the costs and associated healthcare resource assumed for the intervention and comparators in this decision problem.

Table 97: Unit costs associated with the treatments in the economic model

Items	T+D (confidence interval)	Dabrafenib monotherapy	Vemurafenib monotherapy	Reference in submission
Technology cost	Dabrafenib (NHS list price): 28 day supply @ £5,600 (28x75mg: £1,400 | 28x50mg: £933.33) Dabrafenib will be provided to the NHS at a confidentially discounted price. This discount is applied only in estimates in the PAS addendum. Trametinib (NHS list price): 28 day supply = £4,480.00 (30 x 2mg: £4,800 | 7 x 2mg £1,120 | 30 x 0.5mg £1,200 | 7 x 0.5mg £280) Trametinib will be provided to the NHS at a confidentially discounted price. This discount is applied only in estimates in the PAS addendum.	Dabrafenib: see previous. Dabrafenib is currently available to the NHS at a discounted price (confidential). As such, the CEA in the PAS addendum incorporates this discount.	Vemurafenib: (NHS list price): £1,750 per pack (56 tabs) = £7000/month. Vemurafenib is available to the NHS at a discounted price (confidential). As such, the CEA in the PAS addendum incorporates a range of possible discounts to enable a meaningful comparison.	Section 2.3
Dispensing cost/28 days	£13.60	£13.60	£13.60	Section 5.5.5
Treatment initiation (one time)	£400	£400	£400	Section 5.1.1
Other direct medical costs during PFS (including monitoring)	£148/month	£148/month	£148/month	Section 5.1.1
Other direct medical costs during PPS (including follow up)	£389/month	£389/month	£389/month	Section 5.1.1
PSACT	£55,220	£69,618	£65,002	Section 5.5.8
Terminal care	£7,287	£7,287	£7,287	Section 5.1.1

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

5.6.1. Variables included in the cost-effectiveness analysis

Table 98 summarises the variables included in the cost-effectiveness analysis.

Table 98: Summary of variables included in the cost-effectiveness analysis

	Trametinib+dabrafenib	Vemurafenib	Dabrafenib
Drug utilisation			
Mg per day of use	300mg dabrafenib 2mg trametinib	1920mg	300mg
RDI medication	Dabrafenib: 0.92 Trametinib: 0.96	0.84	0.93
RDI administration	Dabrafenib: 1.01 Trametinib: 1.00	0.96	0.99
Unit costs			
Costs per mg (list price, £)	Dabrafenib: 0.67 Trametinib: 80	0.13	0.67
Dispensing / 28 days (£)	13.60		
Other PFS costs/month (£)	148		
Other PPS costs/month (£)	389		
PSACT (£)	55,220	65,002	69,618
One off cost (£)			
Therapy initiation	400		
Death	7,287		
Patient starting age in model	55 years		
% male in model	54.4%		
Mean body surface area, m^2	1.93		
Mean body weight (kg)	80.13		
Utility values			
Pre-progression	0.837	0.746	0.789
Post-progression	0.697		

5.6.2. Base-case analysis and the NICE reference case

The approach to modelling is consistent with the NICE reference case.

5.6.3. Model assumptions with justification

Table 99 lists the assumptions in the economic model along with a justification for each.

Table 99: Assumptions in the de novo model and justification for each

Assumption	Justification
The model effectively assumes a class effect (from the efficacy perspective) for the BRAF inhibitors by pooling time to event data from COMBI-v and COMBI-d	Clinical evidence and strong clinical opinion consistently suggest this to be a reasonable and justifiable assumption. See Appendix 8.13.
Treatment duration for trametinib + dabrafenib combination, vemurafenib monotherapy and dabrafenib monotherapy represent exposure data in the respective clinical trials (COMBI-v and COMBI-d trials)	With this approach there is no requirement to make assumption about duration of treatment. Progression and treatment costs reflect potential treatment interruptions and discontinuations.
Utility data used to value the health states are based on direct patient assessments in the head-to-head trials (COMBI-v and COMBI-d)	EQ-5D data directly from a randomised trial of targeted agents was considered more robust than relying on literature. The utilities in this model are comparable with those used in recent appraisals of metastatic melanoma treatments.
30 years approximates a lifetime horizon	The mean age of patients in economic model is 55 years; a 30-year horizon was considered adequate to represent the patient lifetime.
Only grade 3+ AEs with an incidence of ≥5% or more are included in the model for costing purposes	This approach includes only those adverse events which are potentially costly to treat.
Oral medications are not associated with an administration cost (dispensing costs are included)	The intervention and comparators are likely to be prescribed every 28 days and patients will self-administer treatment; therefore it is reasonable to assume that once dispensed, there are no further costs associated with administering the therapies.
A 28-day supply of dabrafenib, trametinib or vemurafenib is dispensed every 28 days	This assumption was validated with clinical experts during an advisory board for the dabrafenib monotherapy submission and is consistent with the assumption made in the vemurafenib NICE appraisal.
The model assumes that trametinib + dabrafenib therapy, dabrafenib monotherapy and vemurafenib are dispensed every 28-days and that the entire cost of the therapy is incurred at the start of the 'cycle'; implicit in this is the assumption that any unused medication would be discarded if the patient discontinues treatment partway through a 28-day 'cycle'	This assumption is likely to reflect real life use of these medicines, i.e. that a patient's prescription is not used by another patient following discontinuation.
By implementing relative dose intensities, the model assumes that patients with treatment interruptions retain and use unused medication from prior cycles in subsequent ones	Again, this assumption is likely to reflect real life use of these medicines (which are dispensed in 7-day packs), i.e. that patients will not discard their medication if they down dose during a 28-day period.

5.7. Base-case results

5.7.1. See below

Base-case incremental cost effectiveness analysis results

5.7.2. Summary base-case results

Basecase pairwise and incremental analyses for trametinib + dabrafenib combination versus vemurafenib and dabrafenib are presented in Table 100 and Table 101 below.

NB: Results presented in the submission document are based on intervention and comparator list prices. Comparable results including all relevant patient access schemes are presented in the confidential PAS addendum.

Consideration of dabrafenib/trametinib combination under NICE's criteria for life-extending, end of life medicines

The combination of dabrafenib and trametinib meets criteria as a life-extending, end of life therapy, compared with both dabrafenib and vemurafenib monotherapies, fulfilling the specific criteria for such medicines as set out in NICE's Supplementary Advice (2009) on end of life (EOL) medicines. Please see Section 4.13.3 for a further discussion.

Table 100: Base case pairwise analysis of trametinib + dabrafenib versus vemurafenib and versus dabrafenib (not incorporating available discounts)

	Trametinib + dabrafenib	Vemurafenib	Dabrafenib	Trametinib + dabrafenib vs. Vemurafenib	Trametinib + dabrafenib vs. Dabrafenib
Effectiveness, Discounted					
Progression-Free Life Years	1.767	1.101	1.101	0.667	0.667
Post-Progression Life Years	2.818	1.833	1.833	0.986	0.986
Life Years	4.586	2.933	2.933	1.653	1.653
Quality-Adjusted Life Years	3.443	2.098	2.146	1.345	1.298
Costs, Discounted					
Direct Medical					
Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other, Progression-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other, Post-Progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	129,707	135,058
Cost-Effectiveness					
Cost per Life Year				78,489	81,727
Cost per Quality-Adjusted Life Year				**96,437**	**104,069**

Table 101: Incremental analyses (not incorporating available discounts)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Dabrafenib	[redacted]	2.933	2.146	-	-	-	-	-
Vemurafenib	[redacted]	2.933	2.098	5,351	0.000	-0.047	dominated	dominated
Trametinib + dabrafenib combination	[redacted]	4.586	3.443	129,707	1.653	1.345	104,069	104,069

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Costs and benefits are discounted

Clinical outcomes from the model

5.7.3. Consistency of model outcomes with clinical data

Table 102 compares the efficacy outputs of the economic model with results obtained in clinical trials demonstrating consistency between the data sources.

Table 102: Summary of clinical trial and model predicted efficacy

	Trametinib + dabrafenib combination		**Vemurafenib monotherapy**		**Dabrafenib monotherapy**	
	Clinical trial result	*Model result*	*Clinical trial result*	*Model result*	*Clinical trial result*	*Model result*
PFS, months (median)	• COMBI-v trial:12.6 • COMBI-d trial:11.0	11.3	• BRIM-3 trial:6.9 • COMBI-v trial: 7.3	7.4	• BREAK-3 trial: 6.9 • COMBI-d trial: 8.8	7.4
OS, months (median)	• COMBI-v trial:25.6 • COMBI-d trial:25.1	26.3	• BRIM-3 trial: 13.6 • COMBI-v trial: 18.0	18.2	• BREAK-3 trial: 20.1 • COMBI-d trial: 18.7	18.2

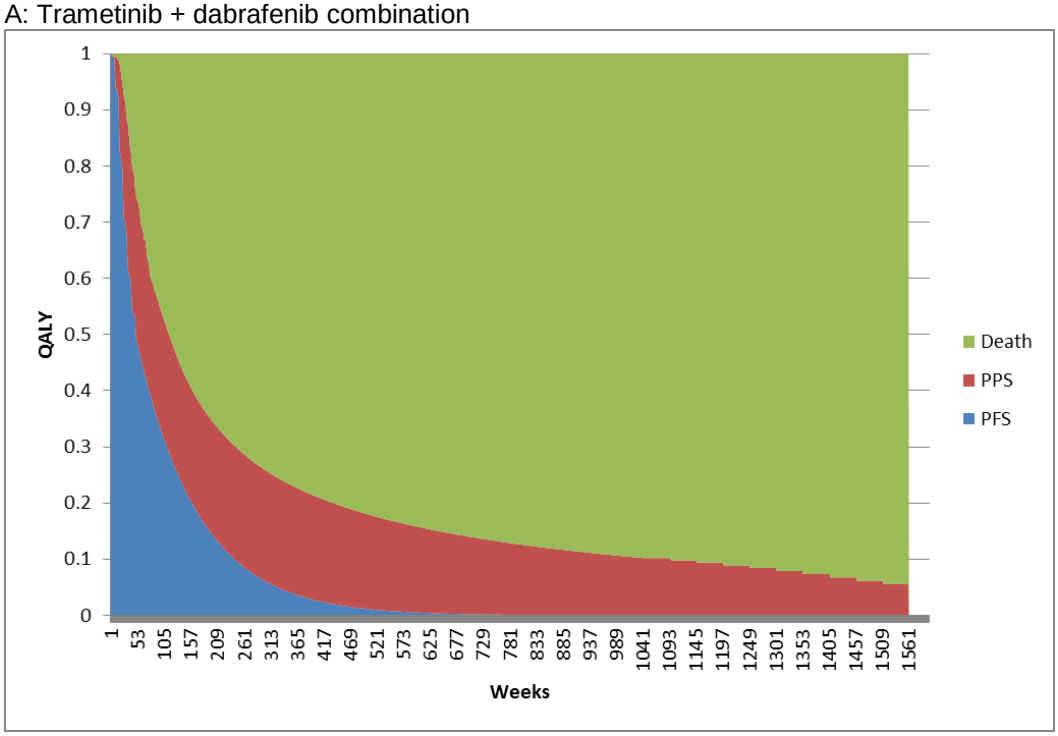
The model predicted median PFS and OS values for the trametinib + dabrafenib combination and for the comparators – vemurafenib monotherapy and dabrafenib monotherapy – are consistent with those reported in clinical trials.

5.7.4. Proportion of cohort in each health state over time (Markov trace)

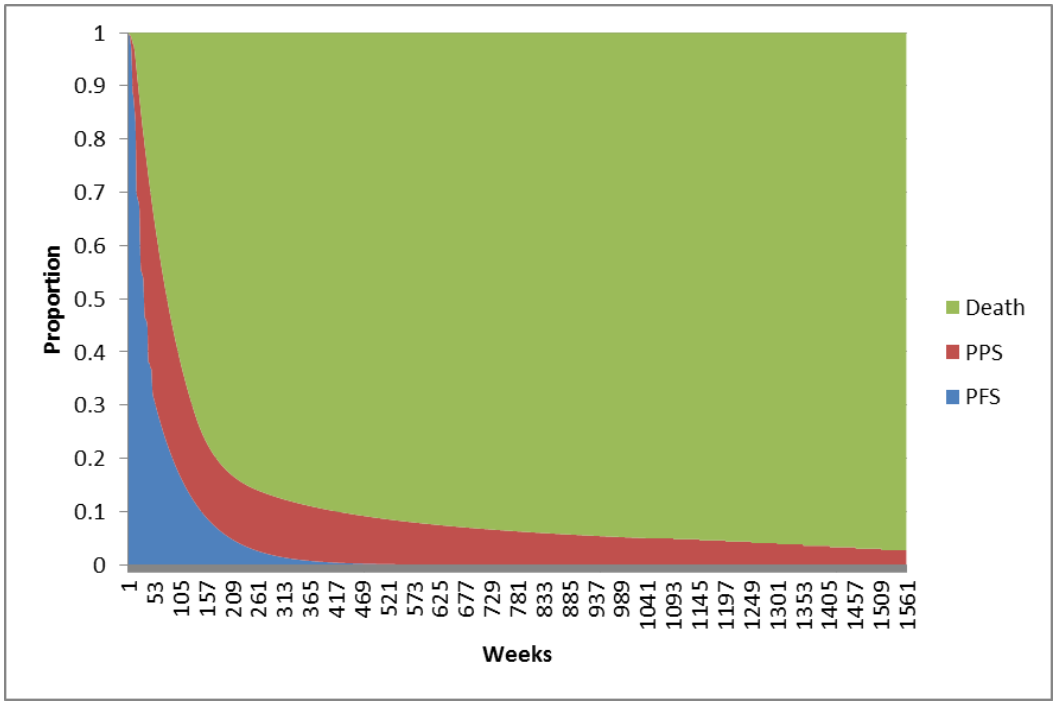
The proportion of the cohort in each health state over time is represented in Figure 36 below.

Figure 36: Proportion of patients in each health state over time

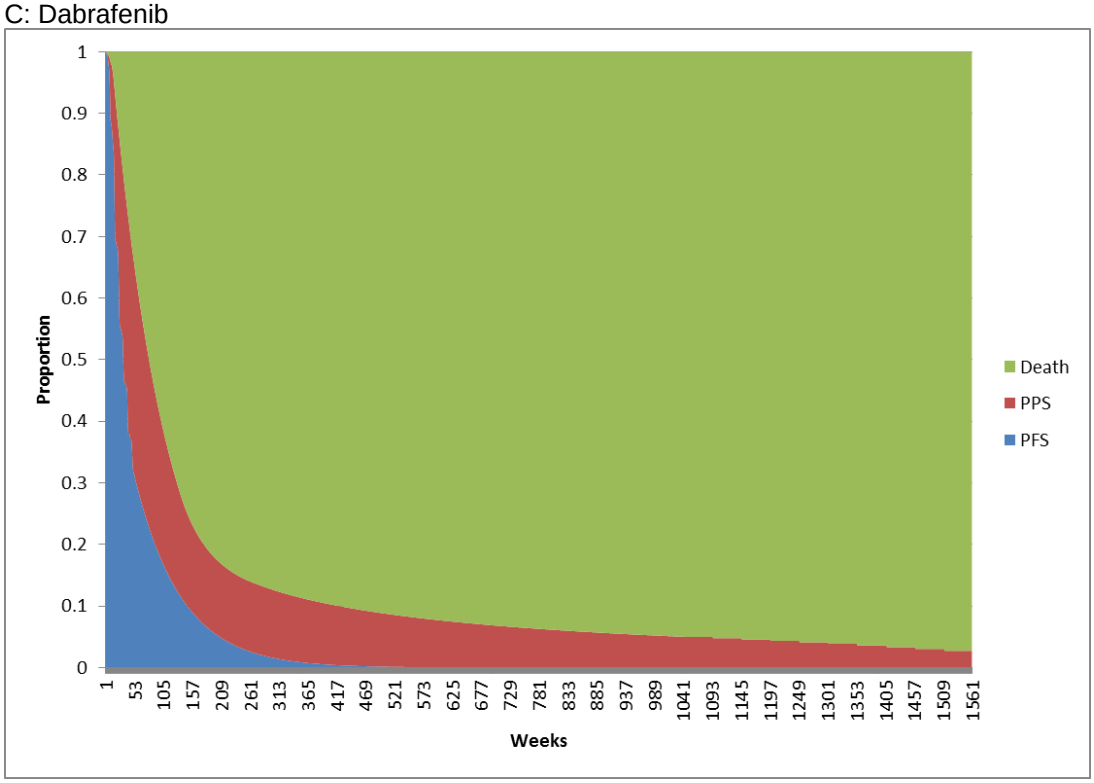
A: Trametinib + dabrafenib combination



B: Vemurafenib



C: Dabrafenib



5.7.5. QALY accrual over time

QALYs are generated in the model on the basis of the proportion of patients and the time spent in each of the health states (PFS, PPS). The proportion of patients over time in each state is estimated through extrapolation as described in Section 5.3.1 above. QALYs are accrued by applying QALY weights to health states.

Disaggregated results of the base case incremental cost effectiveness analysis

5.7.6. QALY and cost accrual over time

Table 103, Table 104 and Table 105 provide the disaggregated QALYs and costs by health state. Cost data is provided with no discounts applied (for dabrafenib, trametinib or vemurafenib).

Table 103: Incremental QALYs by health state

		Versus vemurafenib			**Versus dabrafenib**		
Health state	QALY T+D combination	QALY vemurafenib	Increment	% absolute increment (ignoring negatives)	QALY dabrafenib	Increment	% absolute increment
PFS	1.48	0.82	0.66	49%	0.87	0.61	47%
PPS	1.96	1.28	0.69	51%	1.28	0.69	53%
Total	3.44	2.10	1.34	100%	2.15	1.30	100%

Table 104: Incremental costs by health state (no PAS applied)

		Versus vemurafenib			**Versus dabrafenib**		
Health state	Cost T+D combination (£)	Cost vemurafenib (£)	Increment	% absolute increment (ignoring negatives)	Cost dabrafenib (£)	Increment	% absolute increment
PFS	[redacted]	[redacted]	136,361	95%	[redacted]	146,227	93%
PPS	[redacted]	[redacted]	-6,654	5%	[redacted]	-11,169	7%
Total	[redacted]	[redacted]		100%	[redacted]		100%

Table 105: Incremental costs by category of cost (no PAS applied)

		Versus vemurafenib			Versus dabrafenib		
Health state	Cost T+D combination (£)	Cost vemurafenib (£)	Increment (£)	% absolute increment (ignoring –ves)	Costs dabrafenib (£)	Increment (£)	% absolute increment (ignoring –ves)
Medication	[redacted]	[redacted]	134,948	94%	[redacted]	144,704	92%
Administration	[redacted]	[redacted]	448	0%	[redacted]	442	0%
Adverse Events	[redacted]	[redacted]	-219	0%	[redacted]	-103	0%
Other PF costs	[redacted]	[redacted]	1,184	1%	[redacted]	1,184	1%
Other PP costs	[redacted]	[redacted]	-6,654	5%	[redacted]	-11,169	7%
Total	[redacted]	[redacted]		100%	[redacted]		100%

5.8. Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was undertaken by sampling simultaneously from the estimated probability distributions of the model parameters to obtain 1000 sets of model input estimates.

For each simulation, expected costs and QALYs were calculated for each comparator, along with the differences between comparators in expected costs and QALYs. 95% CIs were calculated for expected costs and QALYs and the differences in expected costs and QALYs based on the 2.5 and 97.5 percentiles of these simulations. For each comparison, simulation results were plotted on the cost-effectiveness plane. Cost-effectiveness acceptability curves (CEACs) were constructed for pairwise comparisons of each intervention versus the relevant comparators. Additionally, CEACs were constructed on an incremental basis in order to determine the proportion of simulations in which each comparator was cost-effective compared to others.

NB: PSA results presented in the submission document are based on intervention and comparator list prices. Comparable results including all relevant patient access schemes are presented in the confidential PAS addendum.

5.8.1. See below

5.8.2. PSA parameter distributions

Details of the parameter sampling undertaken for PSA are described in Table 106 below.

Table 106: Parameter sampling in probabilistic sensitivity analyses

Parameter	Detail
PFS and OS distributions	Sampled based on bootstrapping. Parametric curves for PFS and OS were fitted using accelerated failure time to a set of 1000 pseudo samples generated from the IPD via sampling with replacement independently from the two underlying trial datasets (i.e. the number of subjects from each trial contributing to each sample was constant across samples). This accounts for the stratification of randomisation by clinical trial which pooling introduces. Survival parameters in the model were then sampled by selecting at random from the bootstrapped parameters. In order to ensure appropriate correlations, all parameters for a comparator were selected from the same bootstrap sample.
Unit costs of study medications and pharmacy dispensing fees	Not sampled; assumed to be known (not random variables)
All other cost parameters	Sampled assuming a lognormal distribution and a standard error of 25% of the base-case value. Cost parameters shared across multiple comparators were sampled jointly once per simulation. Estimates of the variance of the RDIs for medication and administration costs were not available and therefore sampled.
Utility decrements for pre-	Sampled using a lognormal distribution with standard errors based on trial data.

progression vs. perfect health (1-utility value for pre-progression)	Utility decrements shared by multiple comparators were sampled jointly once per simulation. For trametinib + dabrafenib, the utility decrement for post-progression vs. pre- progression was sampled assuming a lognormal distribution. For all other comparators, the utility decrement for vs. progression was solved for such that post-progression utility was the same as that for trametinib + dabrafenib.
Probabilities of AEs	Sampled independently for each AE and comparator using beta distributions. The RRs for the AEs were sampled as lognormal distributions (the SE entered was assumed to be the SE of the log(RR)).

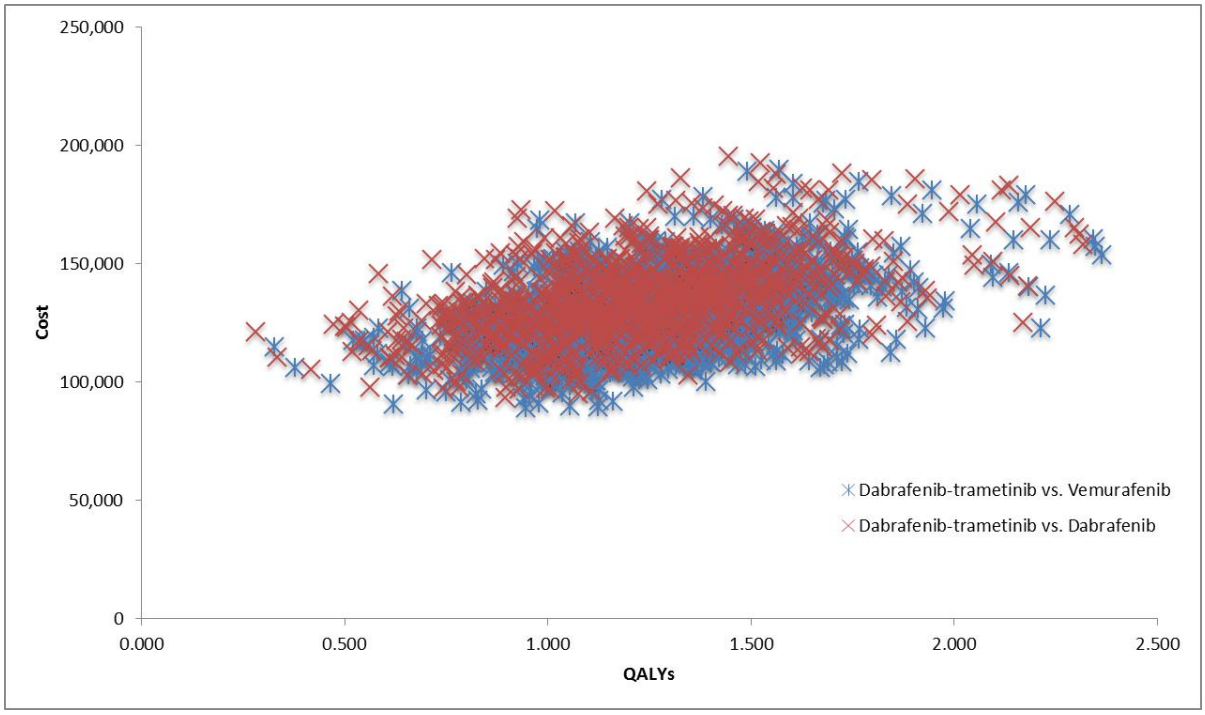
5.8.3. Incremental CE results of PSA

The mean ICERs with 95% CI resulting from the pairwise analyses in the PSA analysis (1000 simulations) are presented below. NB: these results do not incorporate any of the available patient access schemes for the intervention or comparators.

Trametinib + dabrafenib combination	Mean ICER (£)	Lower 95% CI	Upper 95% CI
Versus vemurafenib	101,332	88,720	141,247
Versus dabrafenib	109,380	93,860	159,250

The scatterplot resulting from the PSA for trametinib + dabrafenib versus vemurafenib and versus dabrafenib is presented in Figure 37 below.

Figure 37: Scatter plot: Trametinib + dabrafenib versus vemurafenib and versus dabrafenib (list prices)



Pairwise and incremental acceptability plots are presented below in Figure 38 and Figure 39.

Figure 38: Acceptability curves of pairwise comparisons of trametinib + dabrafenib combination (list prices)

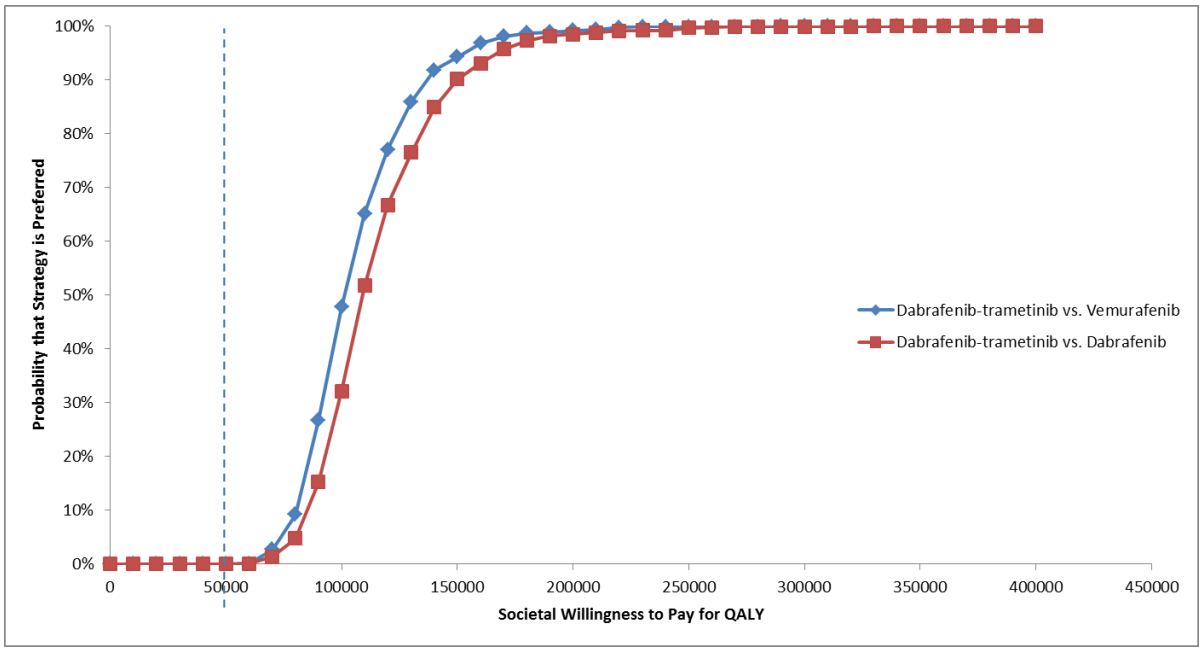
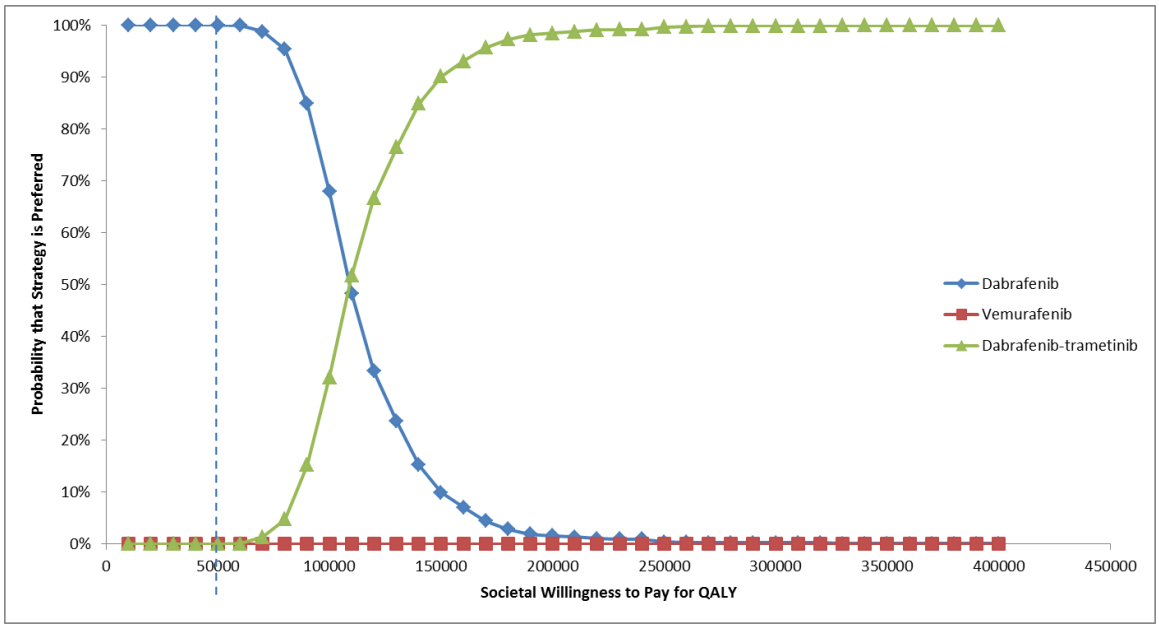


Figure 39: Incremental CEAC for trametinib + dabrafenib combination (list prices)



In this analysis expected costs are higher for trametinib + dabrafenib combination than vemurafenib and dabrafenib monotherapy in 100% of simulations. Expected QALYs are higher for the combination than either monotherapy in 100% of the simulations. Table 107 below presents the probability that the trametinib + dabrafenib combination is cost-effective at an acceptability threshold of £50,000/QALY (see Section 4.13.3).

Table 107: Summary of PSA for trametinib + dabrafenib combination (list prices)

QALY threshold	Probability that trametinib + dabrafenib combination is cost-effective versus comparator (%)	
	Vemurafenib	Dabrafenib
£50,000	0%	0%

5.8.4. Variability between basecase and PSA

The PSA results are broadly consistent with the results presented in the base case (T+D versus vemurafenib: £101,331/QALY in PSA versus £96,437/QALY in base case| T+D versus dabrafenib: £109,380/QALY in PSA versus £104,069/QALY in base case).

Deterministic sensitivity analysis

5.8.5. Details of DSA

Table 108 below details the scenarios investigated in deterministic sensitivity analyses along with a rationale for each set of changes.

Table 108: Deterministic sensitivity analyses

1	Model timeframe 20-40 years	Horizon is a potential sensitivity in the economic model, particularly given the accrual of benefit post progression
2	No continuing benefit assumed for PFS	To determine the impact of this clinically conservative assumption
3	Varying additional pre- and post-progression monthly costs and terminal care costs by +/- 50%	These costs accrue alongside treatment costs and may be important contributors in the assessment of ICERs
4	Varying utility decrement of pre-progression and post-progression versus perfect health to their upper and lower 95%CI bounds	The valuation of the individual health states is likely to have an impact on the overall cost-effectiveness

5.8.6. Results of DSA

Results of deterministic sensitivity analyses based on the above parameters are presented in the form of tornado diagrams representing the individual pairwise comparisons of interest. Figure 40 presents the DSA results for the comparison of trametinib + dabrafenib combination with dabrafenib monotherapy. Figure 41 presents the DSA results for the comparison of trametinib + dabrafenib combination with vemurafenib monotherapy.

The figures suggest that the model is relative insensitive to monthly pre- and post-progression costs as well as the underlying valuation of the health states in the model. The results are sensitive to the time horizon with the longer time horizon improving the ICER for trametinib + dabrafenib versus both dabrafenib and vemurafenib. The no continuing benefit assumption improves the ICERs across both comparisons.

Figure 40: Tornado plot for comparison of trametinib + dabrafenib versus dabrafenib monotherapy

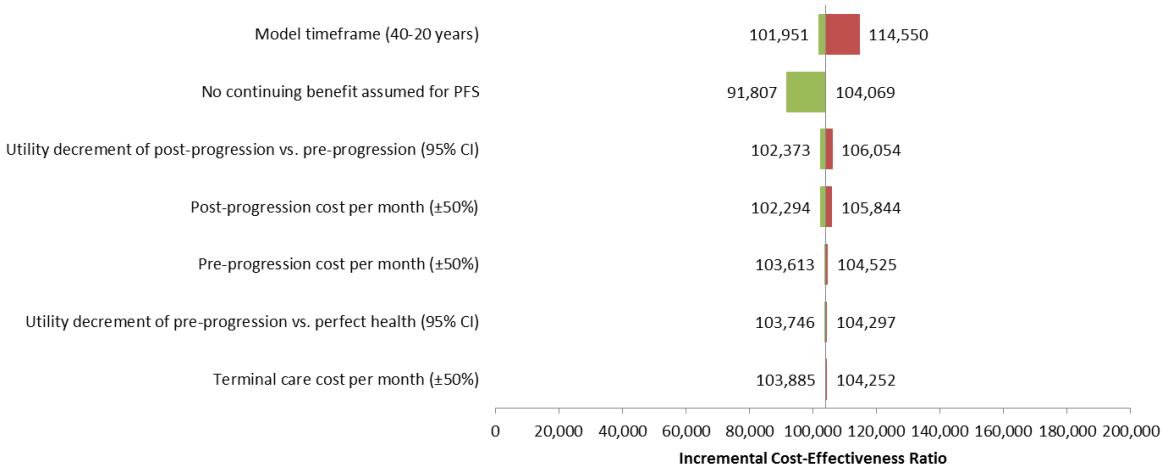
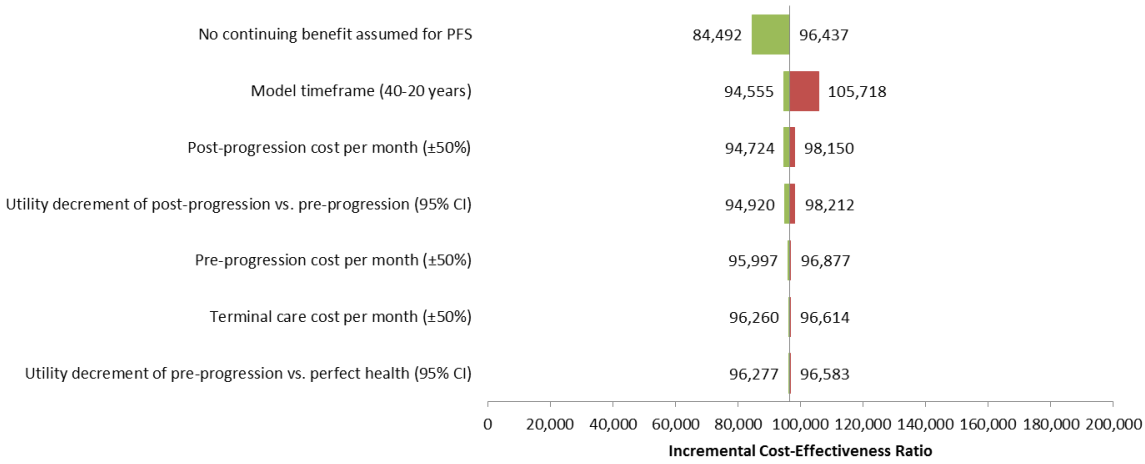


Figure 41: Tornado plot for comparison of trametinib + dabrafenib versus vemurafenib monotherapy



5.8.7. Sensitivity analyses on the basis of unconfirmed pricing

Confidential discounts are currently available to the NHS for both dabrafenib monotherapy and vemurafenib monotherapy. Base case ICERs are estimated assuming intervention and comparator list prices. Analyses which incorporate the proposed confidential prices for dabrafenib and trametinib in combination, the discount available to the NHS for dabrafenib monotherapy and a range of discounts for vemurafenib are incorporated into analyses and presented in the PAS addendum.

Scenario analysis

5.8.8. Structural sensitivity analyses

One scenario analysis was undertaken which explored the underlying assumption of trametinib + dabrafenib's continuing benefit in progression free survival beyond the study follow up.

In the base case the continuing benefit assumption is implemented by assuming that the hazard for PFS in the combination arm (determined by the break point analysis discussed in Section 5.3.1) is constant throughout the projection period (an implied HR for combination versus BRAFi monotherapy of 0.0360/0.0519 = 0.694).

In this scenario analysis it is assumed that the monotherapy exponential projection applies to the combination arm from the end of follow up, i.e. treatment effect of combination on progression disappears after the end of the trial period and monthly hazards of progression for the trametinib-dabrafenib combination in the projection phase become equivalent to the hazards in the BRAF monotherapy arm.

5.8.9. Results of scenario analyses

Pairwise and incremental results of the scenario analyses are presented below.

Table 109: Scenario analysis pairwise analysis of trametinib + dabrafenib versus vemurafenib and versus dabrafenib (not incorporating available discounts)

	Dabrafenib-trametinib	Vemurafenib	Dabrafenib	Dabrafenib-trametinib vs. Vemurafenib	Dabrafenib-trametinib vs. Dabrafenib
Effectiveness, Discounted					
Progression-Free Life Years	1.617	1.101	1.101	0.517	0.517
Post-Progression Life Years	2.968	1.833	1.833	1.136	1.136
Life Years	4.586	2.933	2.933	1.653	1.653
Quality-Adjusted Life Years	3.422	2.098	2.146	1.324	1.277
Costs, Discounted					
Direct Medical					
Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other, Progression-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other, Post-Progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	111,867	117,217
Cost-Effectiveness					
Cost per Life Year				67,693	70,931
Cost per Quality-Adjusted Life Year				**84,492**	**91,807**

Table 110: Scenario analysis : Incremental analyses (not incorporating available discounts)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Dabrafenib	[redacted]	2.933	2.146	-	-	-	-	-
Vemurafenib	[redacted]	2.933	2.098	5,351	0.000	-0.047	dominated	dominated
Trametinib + dabrafenib combination	[redacted]	4.586	3.422	111,867	1.653	1.324	91,807	91,807

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Costs and benefits are discounted

Summary of sensitivity analyses results

5.8.10. Discussion of sensitivity analyses

Sensitivity analyses, assuming the treatments at their list prices, suggest that the model is most sensitive to the time frame assumption and to the continuing PFS benefit assumption. The ICER increases with a reducing time frame as might be expected as some QALYs are accruing in the post-progression state. The continuing benefit assumption is explored in a scenario analysis and a clinically conservative assumption that the PFS benefit linked to combination treatment does not continue beyond trial follow up leads to a reduction the ICERs for both the trametinib + dabrafenib combination versus vemurafenib and versus dabrafenib.

5.9. Subgroup analysis

5.9.1. N/A

5.9.2. Subgroup analyses in the CEA

Specific subgroups are not considered in the economic model.

5.9.3. Characteristics of the subgroups

N/A, no subgroup analyses are presented.

5.9.4. Details of statistical analyses

N/A, no subgroup analyses are presented.

5.9.5. Results of subgroup analyses

N/A, no subgroup analyses are presented.

5.9.6. Other potential subgroups not considered

N/A, no subgroup analyses are presented.

5.10. Validation

5.10.1. Validation of de novo cost-effectiveness analysis

The Excel workbook used for this evaluation is an adaptation of one that has been used in several prior economic evaluations (UK, Australia and Canada). The original model was validated internally by Policy Analysis Incorporated (PAI) by taking the inputs to the model and entering them into a different model, developed by a different analyst at PAI. Results for the validation of model results showed no material differences in measure of costs or effectiveness between the model used in this evaluation and the validation model (i.e. difference between models <.002% for all measures). The original model was also validated independently by investigators at the York Health Economic Consortium. No material differences between the results generated by the PAI model and the YHEC validation model were identified. The main modifications to the model relative to the original model are the streamlining of some calculations and the additional of functionality to use restricted cubic splines for modeling PFS and OS.

YHEC's review included completion of a standard model checklist that entailed a number of checks and 'pressure tests', using extreme values to check the functioning of the model. The tests performed and outcomes of each are shown in Table 111.

Table 111. YHEC checklist for model validation

#	Test	Expected effect	Observed effect
1	Set initial number of patients to 0	Costs and QALYs equal 0 across treatments	N/A
2	Set initial number of cases to 1	ICER unaltered	N/A
3	Set both treatment and comparator to same intervention	Costs and QALYs to be equal.	N/A
4	Set treatment to 'comparator' and comparator to 'treatment'	Costs and QALYs to be the same as base-case, but inverted.	N/A
6	Set all efficacy data equal for treatment and control and set disutility associated with treatment related adverse events to 0.	Same QALY estimates for treatment and control.	Same QALY estimates for treatment and control.
7	Set mortality rate to 0% at all ages	No deaths in model	No deaths in model
8	Set mortality rate to 100% at all ages	All patients dead at cycle 1but still generate expected costs and QALYs	Test: OS set to 0% for all cycles Result: Patients receive one cycle of costs and less than one cycle of life years
9	Set mortality rate to 100% at age 70	All patients dead after x years (starting age 70 - x) but still generate expected costs and QALYs.	
10	Increase mortality rate	Reduced costs.	Reduced costs.
11	Health state utilities same for all states	Same QALYs for surviving patients (life years and QALYs should have same ratio in both arms)	Same QALYs for surviving patients (life years and QALYs should have same ratio in both arms)

12	Health state utilities and adverse events all set to 0.	Total QALYs = 0 for treatment and comparator.	Progression-Free Decrement vs. Perfect Health set to 1. Total QALYs = 0
13	Health state utilities for states all set to 1 and adverse events all set to 0	Total QALYs same as life years	Utility decrement set to 0 for all health states. Total QALYs same as LYs.
15	Unit costs of treatments set to 0.	Total cost of treatment = 0	Total cost of treatment = 0
16	Doubled unit costs of treatment	Treatment costs doubled	Treatment costs doubled
17	Unit costs of administration visit cost and follow-up visit cost set to 0.	Total administration costs = 0.	Total administration costs = 0.
18	Doubled unit costs of administration visits and follow-up visits	Total administration costs doubled	Total administration costs doubled
22	Alter time horizon	Total costs and QALYs to increase/decrease in accordance with longer/shorter durations.	Total costs and QALYs increase/decrease in accordance with longer/shorter durations.
23	Altered subgroups	Varies by model	N/A
25	Altered transition probabilities	Varies by model	N/A
26	Discount rates set to 100%	Costs and QALYs should be significantly reduced	Costs and QALYs significantly reduced
27	Discount rates set to 0%	Undiscounted and discounted results should be the same	Effectiveness outputs: undiscounted and discounted results are the same. Cost outputs: 0% discount rate results in higher costs.

Since the YHEC's validation, a number of changes have been made to the model to streamline calculations and to add functionality. In particular, functionality was added to allow for RCS survival distriutions. The distributions generated by the model match those generated by the R program used to derive the parameter estimates.

The model was validated by a third party - PRMA Consulting – who tested the accuracy and robustness of the model under the following components (where available or reported)

- Process checklist for the development of cost-effectiveness models
- Model preparation
- Model development
- Model structure
- Model inputs
- Model execution and analysis
- Model checking
- Internal validity checklist for cost-effectiveness models
- Model

- Macros
- External validity checklist for cost-effectiveness models
- Model reporting and communication
- Model report
- CHEERS checklist.

In summary this review found no errors but concluded that ease of access or use may be low and the source of many input parameter values were unclear. As a result a significant effort has gone in to improving the usability of the economic model by stripping our superfluous functionality and providing clear transparent descriptions in this report of all model inputs.

5.11. Interpretation and conclusions of economic evidence

The systematic literature review undertaken for this appraisal did not identify any directly relevant cost-effectiveness analyses of the trametinib + dabrafenib combination (the one identified had several limitations which make a direct comparison meaningless) and as such, the results presented here cannot be benchmarked against other studies.

However, the analysis which underpins the economic assessment in this submission is based upon two high quality, robust, randomised controlled trials including more than 560 patients treated with the trametinib + dabrafenib combination and a comparable number treated with BRAF inhibitor monotherapies, directly addressing comparisons of relevance to the decision problem.

Both of the underlying studies – COMBI-d and COMBI-v – were multi-centre trials and included centres in the United Kingdom. In addition, costs incorporated into the economic model are specific to practice in the UK and based on NHS Reference costs. As such, the analysis is generalisable to the populations of England and Wales and addresses fully the specifications in the decision problem.

The strengths and limitations of the evaluation are presented in Table 112 below.

Table 112: Strengths and limitations of the economic evaluation

Strengths	An assessment of this economic analysis on the basis of the critical appraisal checklist by Drummond and Jefferson, Philips and colleagues, and the NICE reference case is provided in Appendix 8.20. This assessment meets all of these standard quality criteria. In addition: • The economic analysis utilises an established modelling methodology used in previous assessments of medicines for patients with metastatic melanoma • The pooling of PFS and OS data from two robust, randomised controlled trials – COMBI-d and COMBI-v – strengthens the AUC analyses and yields a more precise estimate of the effect of combination versus monotherapy; we have provided the clinical and evidence rationale for why the underlying assumption of a class effect for the BRAF inhibitor monotherapies is reasonable for this analysis. • As there is no known way to account for stratification in the Kaplan-Meier, break point

	analyses and combination of KM and exponential curves, the impact of heterogeneity was accounted for in PSA. Other parameters – RDIs, PSACT costs and utility values are incorporated with an approach analogous to adjusted indirect treatment comparisons in which randomisation is maintained. • Kaplan-Meier and exponential distributions of OS for each treatment arm were combined with case-mix adjusted survival data from the AJCC melanoma registry, and general population mortality data (incorporating the increased hazard of death in the metastatic melanoma population). AJCC data arguably represent the best source of long term survival data for patients with metastatic melanoma receiving standard treatment and therefore add external validity to the model projections. • The underlying approaches to modelling have been previously proposed by the ERG. • The model predicts clinical outcomes that are comparable to those seen in clinical trials. This gives reassurance that the predicted benefit of the trametinib + dabrafenib combination is not overestimated. • The model accounts for the costs of post-study anti-cancer therapy. • The model incorporates a comprehensive range of scenario analyses in DSA. • Utility data were derived for treatment and intervention directly from phase III studies in BRAFV600 mutation-positive metastatic melanoma patients being treated with targeted therapies; this eliminates the need to model impact of AEs as these are already incorporated.
Limitations	Certain limitations must be acknowledged: • The main limitation of this study is the lack of PFS and OS data from the COMBI-d and COMB-v trials beyond approximately 2.5 years. Estimates of the effect of trametinib + dabrafenib combination on PFS and OS are therefore based on projections which combine information from the trials with mortality data from the AJCC Melanoma Registry, as well as UK general population mortality data. Given the inherent uncertainties in such projections, the precise magnitude of treatment effects of trametinib + dabrafenib combination on PFS and OS are associated with uncertainty. • OS projections from 5 to 20 years are based on data from the AJCC Melanoma registry. While these data are arguably the most robust publically available source of data on long-term survival in patients with metastatic melanoma, they are more than a decade old and represent outcomes before the advent of targeted and immunotherapies. Also, they are based largely on data from a few countries and may not be representative of all populations. • This study used list prices for treatments and comparators. The values of these discounts are confidential and were therefore not used in this analysis. **The results reported herein therefore do not reflect the actual cost-effectiveness of dabrafenib-trametinib to the NHS.** • Estimates of the costs of treatment of AEs were limited to costs of treatment of Grade 3+ AEs with frequency of 5% or more in any arm of COMBI-v or COMBI-d. The analysis did not consider the costs of Grade 1-2 AEs or Grade 3+ AEs with frequency less than 5%, as these AEs are not likely to have substantial costs. Nevertheless, the focus on a limited set of AEs may have led to underestimation of the differences between treatments in costs of AEs. • Estimates of other disease management costs per month of PFS and PPS were based on utilisation estimates from a survey five UK clinicians regarding treatment of individuals in the UK diagnosed with stage III or stage IV melanoma who received active treatment with systemic therapy, outside of a clinical trial, or who received any form of supportive care. Details regarding the methods used for this survey were not

	available and assessment of the validity of the results is difficult. These estimates are not likely to have a material impact on the study findings.

In summary, the robust cost-effectiveness analysis conducted here confirms that when confidential discounts are applied (see the confidential PAS addendum), the combination of trametinib with dabrafenib presents a cost-effectiveness alternative therapy to BRAF inhibitor monotherapy for BRAFV600 mutation positive patients.

6. Assessment of factors relevant to the NHS and other parties

6.1. Patients eligible for treatment in England

The estimated incident population of adults with unresectable or metastatic melanoma with a BRAF V600 mutation is approximately 992 per annum. The estimate is detailed in Section 1 and represents the maximum total population to whom this therapeutic indication applies.

Assuming a population growth of 0.8% per annum, the total eligible population over the next five years is represented in Table 113. This estimate does not account for market share and so represents a *maximum* number of eligible patients. Table 114 presents the likely patient numbers over time with clear assumptions about uptake and market share.

Table 113: Maximum eligible population

Year	2016	2017	2018	2019	2020
Maximum eligible population	992	1000	1008	1016	1024

6.2. Assumptions made about current treatment options and uptake of technologies

The following market share assumptions are applied to the maximum eligible patient population above:

- Increasing market share for trametinib + dabrafenib therapy; [redacted] and [redacted]

Table 114: Likely patient numbers with market share assumptions

Year	2016	2017	2018	2019	2020
Anticipated patients with market share assumptions applied	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

All relevant costs associated with these technologies are incorporated into the budget impact estimates below (which are derived from the economic model) and represent total costs to the NHS assuming that the patient access schemes are implemented.

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

Treatment costs are derived from the economic model; cost inputs are described in detail in Section 5.5.5.

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

The targeted BRAF inhibitor monotherapies - vemurafenib and dabrafenib – are the current standard of care for patients with BRAF V600 mutation positive metastatic melanoma. We do not anticipate the introduction of the combination of dabrafenib and trametinib to result in considerable resource savings compared to the requirements for these therapies.

6.6. Estimated annual budget impact for the NHS in England

Table 115 below describes the anticipated 5 year budget impact to the NHS of introducing the dual therapy, assuming positive NICE guidance and incorporating patient access schemes for dabrafenib and trametinib. Underlying patient estimates are as described in Table 113 above and it is assumed that these costs will displace those of vemurafenib, not be in addition to them.

Table 115. Anticipated budget impact of introducing dual therapy

Cost	Year 1	Year 2	Year 3	Year 4	Year 5
Anticipated number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition / patient / year ([redacted] £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dispensing / patient / year [redacted] £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment of adverse events / patient / year [redacted] £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other pre-progression costs / patient / year [redacted] £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Estimates are based on drug list prices and do not incorporate available patient access schemes

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

None.

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