STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
BIRC	Blind Independent Review Committee
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CEAC	cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COMBI-d	combination trial of trametinib+dabrafenib vs dabrafenib
COMBI-v	combination trial of trametinib+dabrafenib vs vemurafenib
CS	company submission
CSR	clinical study report
DMC	data monitoring committee
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC-QLQC30	European Organisation for Research and Treatment Cancer Quality of Life Questionnaire
EQ-5D	European Quality of Life-5 Dimensions questionnaire
ERG	Evidence Review Group
FACT-M	Functional Assessment of Cancer Therapy - Melanoma
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost effectiveness ratio
IDMC	Independent data monitoring committee
INV	local investigator assessment
irRC	immune-related response criteria
IPCW	Inverse Probability Censored Weighting
IRO	integrated radiology and oncology analysis (central assessment)
ITC	indirect treatment comparison
ITT	intention-to-treat
IVRS	interactive voice recognition system
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
MEK	mitogen-activated protein kinase
MHRA	Medicines and Healthcare Products Regulatory
NICE	National Institute for Health and Care Excellence
ORR	overall response rate
OS	overall survival
PD	progressed disease
PFS	progression-free survival
PPS	post-progression survival
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality adjusted life year
RCT	randomised controlled trial
RPSFTM	Rank-Preserving Structural Failure Time Model
SAE	serious adverse event
SAP	statistical analysis plan

1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Novartis Pharmaceuticals UK Ltd in support of the use of trametinib (Mekinist®) combined with dabrafenib (Tafinlar®) for the treatment of patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma.

Trametinib combined with dabrafenib (trametinib+dabrafenib) is licensed in Europe for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

1.1 Critique of the decision problem in the company submission

The intervention specified in the NICE scope is trametinib in combination with dabrafenib (trametinib+dabrafenib). This combination of drugs received a European marketing authorisation in August 2015 for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Line of treatment is not specified in the licence. Trametinib is available as film-coated tablets and dabrafenib is available as hard capsules. The company estimates that, if recommended by NICE, a maximum of 992 patients per year, in England, would be eligible for treatment with trametinib+dabrafenib.

The comparators specified in the NICE scope are the two BRAF inhibitor monotherapies, dabrafenib and vemurafenib. Vemurafenib was recommended by NICE in December 2012 for the treatment of locally advanced or metastatic V600 mutation-positive melanoma and dabrafenib was recommended by NICE in October 2014 for the treatment of unresectable or metastatic BRAF V600 mutation-positive melanoma. Dabrafenib is available as 75mg capsules and vemurafenib as 240mg tablets.

The patient population specified in the NICE scope, the patient population considered in the company submission (CS) and the patient population described in the trametinib+dabrafenib European licence are identical, i.e. adults with unresectable or metastatic BRAF V600 mutation-positive melanoma.

It is stated in the final NICE scope that, if evidence allows, consideration should be given to the effectiveness of trametinib+dabrafenib as a first-line therapy or after treatment with immunotherapy. The clinical evidence presented in the CS comes from two Phase III randomised controlled trials (RCTs), COMBI-d and COMBI-v. The company did not present

evidence to support the use of trametinib+dabrafenib following treatment with ipilimumab or other immunotherapies.

The extent to which the submitted evidence reflects clinical practice is limited by the fact that patients included in the COMBI-d and COMBI-v trials all had an Eastern Oncology Cooperative Group (ECOG) performance status (PS) of 0 or 1 and no brain metastases. Clinical advice to the ERG is that both patients with an ECOG PS>1 and those with brain metastases are treated in UK clinical practice.

The treatment algorithm presented in the CS suggests that first-line treatment for the patient population being considered in this appraisal is either a BRAF inhibitor or ipilimumab; second-line treatment for those having received a BRAF inhibitor first-line being ipilimumab, and vice versa. It is recognised within the final NICE scope that trametinib+dabrafenib may be prescribed following treatment with an immunotherapy.

Clinical advice provided to the ERG suggests that current NHS clinical practice for the treatment of patients with BRAF mutation-positive disease is uncertain for those patients who are relatively well with slowly progressing disease, i.e. for the patients in the COMBI-d and COMBI-v trials. The treatment options currently available in the NHS include immunotherapy and BRAF inhibitors. Clinical advice to the ERG is that, for patients with BRAF mutation-positive disease who are relatively unwell with rapidly progressing disease, treatment is always a BRAF inhibitor.

The findings from the COMBI-d and COMBI-v trials are only relevant to the cohort of patients in clinical practice with BRAF mutation-positive disease who have an ECOG PS 0-1 and no brain metastases. Clinical advice to the ERG is that some of these patients could have been treated with an immunotherapy instead of a BRAF inhibitor. It is not known whether trametinib+dabrafenib is more effective than an immunotherapy in this group of patients as there are no data available to allow this comparison to be undertaken.

The ERG notes that there is uncertainty around whether pembrolizumab and ipilimumab should have been specified as comparators in the final NICE scope. In previous NICE appraisals, immunotherapy has been a comparator alongside BRAF inhibitor monotherapies for the first-line treatment of people with BRAF mutation-positive melanoma. However, the ERG is also aware that expert clinician opinion may agree with the wording in the final NICE scope for this appraisal i.e. that only dabrafenib and vemurafenib are relevant comparators. Our clinical expert has told us that immunotherapy is only considered as a treatment option

for a very specific group of patients as a first-line treatment, and is more likely to be considered as second-line treatment, after a BRAF inhibitor, on disease progression.

The ERG recognises that there is currently no direct clinical evidence to compare these treatments in either before or after treatment with trametinib+dabrafenib. Furthermore, although indirect treatment comparisons could have been undertaken, the results from such analyses would have been unreliable. Expert clinical advice to the ERG is that, where appropriate, clinicians currently tend to favour treatment with pembrolizumab over ipilimumab because it is efficacious in a larger population of patients and its use is associated with fewer adverse events (AEs).

Clinical evidence is presented in the CS for all five outcomes specified in the final NICE scope: overall survival (OS), progression-free survival (PFS), overall response rate (ORR), AEs and health-related quality of life (HRQoL). These are all outcomes that are commonly measured in metastatic melanoma drug trials.

The company has not identified any equality issues. However, the company has presented a case for trametinib+dabrafenib to be assessed against the NICE End of Life criteria.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a broad literature search and identified two relevant Phase III RCTs (COMBI-d, COMBI-v). Supportive evidence from one Phase II RCT (BRF113220 Part C) was also presented.

The double-blind COMBI-d trial compared trametinib+dabrafenib (n=211) with dabrafenib+placebo (n=212) in patients with previously untreated unresectable or metastatic BRAF V600 mutation-positive melanoma. At the time of the August 2013 analysis, median investigator-assessed PFS was 9.3 months in the trametinib+dabrafenib arm and 8.8 months in the dabrafenib+placebo arm, a difference of 0.5 months (hazard ratio [HR]=0.75, 95% CI: 0.57 to 0.99, p=0.035). At this time point median OS had not been not reached in either arm. At the time of the (unplanned) January 2015 analysis, median PFS was 11 months in the trametinib+dabrafenib arm and 8.8 months in the dabrafenib+placebo arm (HR=0.67, 95% CI: 0.53 to 0.84, p=0.0004). Median OS was 25.1 months in the trametinib+dabrafenib arm and 18.7 months in the dabrafenib+placebo arm, a difference of 6.4 months (HR=0.71, 95% CI: 0.55 to 0.92, p=0.0107). All of the subgroup analysis results of PFS and OS were consistent with the results of the intention to treat (ITT) analyses. The ORR was higher in the trametinib+dabrafenib arm than in the dabrafenib+placebo arm at the time of the August 2013 analysis (67% versus 51% respectively) and at the time of the

January 2015 analysis (69% versus 53% respectively). The results from the analyses of the EQ-5D questionnaire data collected during the COMBI-d trial show that the only time point at which there was a statistically significant difference in utility scores between treatment arms (which favoured trametinib+dabrafenib treatment) was at week 16.

The open-label COMBI-v trial compared trametinib+dabrafenib (n=352) with vemurafenib monotherapy (n=352) in patients with previously untreated unresectable or metastatic BRAF V600 mutation-positive melanoma. At the time of the April 2014 interim analysis, median OS in the trametinib+dabrafenib arm had not been reached and OS in the vemurafenib monotherapy arm was 17.2 months (HR=0.69, 95% CI: 0.53 to 0.0.89, p=0.005). All of the subgroup analysis of PFS and OS were consistent with the results of the ITT analyses. At the time of the March 2015 analysis, median OS in the trametinib+dabrafenib arm was 25.6 months compared with 18 months in the vemurafenib monotherapy arm, a difference of 7.6 months. (HR=0.66, 95% CI: 0.53 to 0.81, p<0.001). The OS HR adjusted for treatment crossover (by 6% of patients) was 0.63 (95% CI: 0.50 to 0.79). Median PFS was 12.6 months in the trametinib+dabrafenib arm and 7.3 months in the vemurafenib monotherapy arm (HR=0.61, 95% CI: 0.51 to 0.73, p<0.001). The ORR was higher in the trametinib+dabrafenib arm than in the vemurafenib monotherapy arm at the time of the April 2014 analysis (64% versus 51%) and at the time of the March 2015 analysis (66% versus 53%) analyses. The results from analyses of EQ-5D questionnaire data showed that, at all assessment points, the differences between utility scores for the two treatment arms were found to be statistically significantly better (p<0.05), and clinically meaningful, for patients treated with trametinib+dabrafenib compared with those for patients treated with vemurafenib monotherapy.

Results from the COMBI-d trial show that the incidence of grade 3 or 4 AEs was slightly lower for patients receiving trametinib+dabrafenib than for patients receiving dabrafenib+placebo (45% versus 50%). Similarly, results from the COMBI-v trial show that the incidence of grade 3 or 4 AES was slightly lower for patients receiving the combination treatment than it was for patients receiving vemurafenib monotherapy (57% versus 66%). In addition, patients treated with trametinib+dabrafenib experienced substantially fewer new skin cancers compared with patients treated with a BRAF inhibitor.

However, treatment with trametinib+dabrafenib appears to be less tolerable than dabrafenib monotherapy. The incidence of AEs leading to permanent discontinuation of study treatment was higher in the combination arm than in the dabrafenib+placebo arm of the COMBI-d study (11% versus 7%). Proportions of patients requiring dose interruptions due to AEs were also higher in the combination arm than in the dabrafenib+placebo arm (56% versus 37%).

In addition, dose reductions due to AEs were higher in the combination arm than in the dabrafenib arm (33% versus 39%).

The company did not present any indirect clinical effectiveness evidence.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG is satisfied with the company's search strategy and stated inclusion and exclusion criteria. The ERG is confident that the searching was carried out to an acceptable standard and is not aware of any additional studies that should have been included in the CS.

1.3.1 Direct evidence

The ERG considers that the COMBI-d trial was well-designed, robust and allowed results to be generated for clinically relevant endpoints. The ERG also considers that the COMBI-v trial is of a good quality. However, this trial was an open-label trial and did not include a blinded independent review of the important secondary radiological outcomes (PFS and ORR). This suggests that results from the COMBI-v trial may be subject to bias. The ERG also notes that the COMBI-v trial was stopped early for benefit; however, since only 6% of the patients in the vemurafenib arm crossed over to treatment with trametinib+dabrafenib, the ERG does not consider the early stopping to be a cause for concern. Patients (n=72) from UK centres were recruited to both trials. The information provided by the company for all of the trials of trametinib+dabrafenib was clear and comprehensive.

1.4 Summary of submitted cost effectiveness evidence

To allow the cost effectiveness of trametinib+dabrafenib to be compared with that of dabrafenib monotherapy and vemurafenib monotherapy, the company developed a de novo partitioned survival model. The model comprised three mutually exclusive health states: progression-free, post-progression and death. All patients entered the model in the progression-free state. Variants of this model structure have been used in a number of previous STAs that have considered the cost effectiveness of treatments for patients with metastatic melanoma. The model has been developed in Microsoft Excel using a 1-week cycle length and the time horizon is set at 30 years. As recommended by NICE, a discount rate of 3.5% has been used for both costs and outcomes; outcomes are measured in quality adjusted life years (QALYs) and the perspective is that of the UK NHS.

Survival was estimated based on pooled data from three sources: the COMBI-d and COMBI-v trials, the American Joint Committee on Cancer (AJCC) registry data and UK life tables. The company has assumed that dabrafenib and vemurafenib are equally efficacious and that

patient outcomes from these two treatments only differ in terms of AE profiles and HRQoL. Utility values used in the company model were calculated from data collected during the COMBI-d and COMBI-v trials. Resource use and costs were estimated based on information collected during the COMBI-d and COMBI-v trials, published sources (including previous STAs) and clinical expert opinions.

The cost effectiveness results presented in the CS are those generated using list prices for all drugs. Department of Health Patient Access Scheme (PAS) discounts have been agreed for trametinib, dabrafenib and vemurafenib, with the PAS for trametinib+dabrafenib expected to be agreed prior to the first NICE Appraisal Committee meeting for this STA. Cost effectiveness results using the PAS prices are presented in an addendum to this report.

The company's base case cost effectiveness results for the comparison of trametinib+dabrafenib therapy with dabrafenib suggest that treatment with the combination therapy leads to a lifetime increase in cost to the UK NHS of £135,058 per patient. In addition, such treatment offers an additional 1.653 life years (LYs) and 1.298 QALYs per patient. The resultant incremental cost effectiveness ratio (ICER) for this comparison is £104,069 per QALY gained.

The company's base case cost effectiveness results for the comparison of trametinib+dabrafenib therapy with vemurafenib suggest that treatment with the combination therapy leads to a lifetime increase in cost to the UK NHS of £129,707 per patient. In addition, such treatment offers an additional 1.653 life years and 1.345 QALYs per patient. The resultant ICER for this comparison is £96,436 per QALY gained.

The company carried out a range of deterministic sensitivity analyses. The results show that the most influential variables were the model time frame and the assumption that there is no continuing benefit for patients receiving trametinib+dabrafenib beyond the trial follow-up period for PFS. One scenario analysis was presented. This explored the impact of assuming no continuing benefit for patients receiving trametinib+dabrafenib therapy beyond the study follow-up period. Results from this analysis suggest that decreasing the effectiveness of trametinib+dabrafenib therapy leads to an increase in its cost effectiveness when compared with dabrafenib or vemurafenib.

1.5 Summary of the ERG's critique of cost effectiveness evidence

The ERG considers that there are several fundamental issues that cast doubt on the cost effectiveness results produced by the company model.

The company model has a flaw in its design whereby the less effective that trametinib+dabrafenib becomes at maintaining patients in a progression free state relative to the comparators, the more cost effective it becomes. This makes meaningful examination of assumptions around effectiveness of trametinib+dabrafenib at preventing disease progression impossible. The ERG considers that the company should have produced a model with differential mortality rates depending on whether patients were in the progression free or progressed state. As a result of this flaw, both the company and the ERG ICERs should be interpreted with caution.

The ERG considers the company's projection for OS on BRAF inhibitor monotherapy to be implausible; the mortality risk at 5 years for patients on BRAF inhibitor monotherapy is higher than the mortality risk derived from analysis of melanoma cancer registry data. In the model higher monthly morality rates are applied to BRAF inhibitor monotherapy for 5 years compared to the mortality risk associated with trametinib+dabrafenib despite most patients stopping any therapy after one year and clinical trial evidence that there is no difference in post treatment survival between trametinib+dabrafenib and BRAF inhibitor monotherapy.

The company has therefore substantially underestimated the survival of patients receiving BRAF inhibitor monotherapy by overestimating the monthly hazard and has therefore substantially underestimated the size of the ICER for trametinib+dabrafenib compared to BRAF inhibitor monotherapy.

The ERG remodelled OS using a more parsimonious approach that assumed equal hazard rates by 27 months for trametinib+dabrafenib and BRAF inhibitor monotherapy and making full use of available trial data. The resultant ICER for trametinib+dabrafenib compared to dabrafenib was £150,821 per QALY gained and compared to vemurafenib was £137,373 per QALY gained.

As the COMBI-v trial was an open-label trial without a placebo and the COMBI-d trial was blinded and placebo controlled, the ERG considers that a better estimate of OS is generated by looking at the unblinded, placebo controlled data from the COMBI-d trial only, rather than the pooled data from the COMB-d and COMBI-v trials. Survival was lower in the vemurafenib arm of the COMBI-v trial compared to survival in the dabrafenib arm of the COMBI-d trial. This may be explained by the lack of a placebo effect in the vemurafenib arm of the COMBI-v trial and by the smaller proportion of patients in the COMBI-v trial continuing on treatment post-progression, these patients also stayed on treatment for a shorter amount of time post progression than patients in the COMBI-d trial. The ERG considers this latter effect to have been likely due to the open-label design of the COMBI-v trial.

The use of PFS data to estimate treatment costs, rather than time to treatment discontinuation (TDD) data underestimates the cost of trametinib+dabrafenib treatment.

As over 25% of patients continued on treatment post progression in both trials, time to treatment discontinuation was a more appropriate outcome to measure the costs of treatment and utility whilst on treatment. The ERG considered that the application of post-study anti-cancer therapy (PSACT) costs should be equal across all arms as there is no statistical or clinical justification for the application of differential utility values for patients receiving different treatments.

The company applied differential utility values for the PFS state depending on treatment arm. There was no robust statistical basis for this assumption and the ERG considered that utility values should be applied to patients whilst on treatment and off treatment rather than based on progression status. The ERG applied just two utility values in the model – one for 'on treatment' and one for 'off treatment'. The two values were independent of treatment arm. The ERG used only data from European patients in the COMBI-d trial to estimate utility values.

Application of the ERG changes to OS, costs and utility but using pooled data from the COMBI-d and COMBI-v trials for OS resulted in an ICER for trametinib+dabrafenib compared to dabrafenib of £202,674 per QALY gained and for trametinib+dabrafenib compared to vemurafenib of £188,965 per QALY gained. If only data from the COMBI-d trial for OS are used then the ICER for trametinib+dabrafenib compared to dabrafenib of £238,277 per QALY gained and for trametinib+dabrafenib compared to vemurafenib of £220,069 per QALY gained.

1.6 Summary of company's case for end of life criteria being met

The company has put forward a case that trametinib+dabrafenib meets NICE's end of life criteria:

- Patients have a life expectancy of less than 24 months. The company cites median OS data from patients recruited to the BRAF inhibitor monotherapy arms of four RCTs (COMBI-d, COMBI-V, BREAK-3 and BRIM-3). The median OS from the trials ranges from 13.6 months to 20.1 months
- The treatment offers an extension to life, normally of at least 3 months compared to current NHS treatment. The company cites the median OS gain for patients recruited to the COMBI-d (trametinib+dabrafenib vs dabrafenib+placebo) and COMBI-v (trametinib+dabrafenib vs vemurafenib) trials. Median OS gain is 6.4 months and 7.6 months respectively
- The treatment is licensed for a small population. The company estimates that 992 patients per annum in England are eligible for treatment with trametinib+dabrafenib.

1.7 ERG commentary on End of Life criteria

The ERG agrees with the company that treatment with trametinib+dabrafenib offers an extension to life of more than 3 months when compared to BRAF inhibitor monotherapy and also agrees that the eligible patient population is small. The ERG notes that the median OS for patients is likely to be as claimed by the company; however, when mean OS is considered, treatment with a BRAF inhibitor monotherapy may increase patient life expectancy to 3 about years.

1.8 ERG commentary on the robustness of evidence submitted by the company

1.8.1 Strengths

Clinical evidence

- The company provided a detailed submission that fulfilled the requirements of the NICE scope
- The ERG's requests for further clinical information were fulfilled promptly and to a good standard
- The clinical evidence presented in the CS is clear and comprehensive
- The COMBI-d and COMBI-v trials recruited substantial numbers of patients and included patients from UK centres
- The OS outcomes from the COMBI-d and COMBI-v trials are largely uncontaminated by patient crossover. Crossover was not permitted in the COMBI-d trial and although allowed in the COMBI-v trial, only 6% of patients crossed over to trametinib+dabrafenib
- Results from the COMBI-d and COMBI-v trials suggest that the median OS for patients treated with trametinib+dabrafenib is between 6.4 (COMBI-d) and 7.6 (COMBI-v) months longer than that for patients treated with dabrafenib or vemurafenib respectively
- Results from the COMBI-d and COMBI-v trials demonstrate that compared with dabrafenib and vemurafenib monotherapies, treatment with trametinib+dabrafenib resulted in fewer incidences of skin-related carcinomas.

Cost effectiveness evidence

- The economic model is largely well described within the CS.

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- There is no clinical evidence to support the use of trametinib+dabrafenib in patients who have received prior treatment in the metastatic setting

- There is no clinical evidence to support the use of trametinib+dabrafenib in patients with a PS of 2 or higher, or for patients with brain metastases
- In current clinical practice, ipilimumab and pembrolizumab are treatment options recommended by NICE for patients with unresectable or advanced BRAF V600 mutation-positive melanoma. The ERG considers that the absence of these comparators limits the relevance of this appraisal to the NHS
- The treatment sequence of BRAF inhibitors and immunotherapy in patients with BRAF mutation-positive melanoma is uncertain. Patients recruited to the COMBI-d and COMBI-v trials appear to be fitter patients who, in clinical practice, could have received an immunotherapy (pembrolizumab or ipilimumab) as a first-line treatment
- The COMBI-v trial was an open-label, unblinded RCT that did not include a blinded independent assessment of radiological outcomes; the extent to which this may have caused trial results to be biased is unclear
- The company has not considered published evidence describing the effectiveness of dabrafenib or vemurafenib other than that resulting from the COMBI-d and COMBI-v trials.

Cost effectiveness evidence

- The company failed to provide a number of the analyses requested by the ERG during the clarification process
- The long-term projections of OS developed by the company lack credibility as they are based on data that were collected prior to the availability of immunotherapy or BRAF inhibitor treatments
- The use of PFS data, rather than TDD data underestimates the cost of trametinib+dabrafenib treatment
- The company model has a structural flaw: the less effective trametinib+dabrafenib becomes at delaying treatment progression, the more cost effective the combination therapy is compared to BRAF inhibitor monotherapy
- The company failed to use scenario analysis to explore any of the assumptions they make on their OS projection, on utility values chosen or on PSACT costs
- The company model does not reflect the current treatment pathway post progression for NHS patients
- The approach used to model OS for patients receiving a BRAF inhibitor lacks credibility
- Study treatment costs have been underestimated and the choice of PSACT costs used by the company is not supported by any statistical evidence
- The company model employs utility values that may be subject to bias.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG suggested five amendments that could be made to the company model. Two amendments offered alternative approaches to the modelling of the OS data. Three amendments suggested changes to the costs and utility values used in the company model. The ERG also noted minor errors related to post-progression monitoring costs, AE costs,

discounting and AJCC case mix adjustment. However, as the impact of correcting these minor errors would only have a small impact on the size of the ICERs, the ERG did not include these minor errors when compiling the list of suggested model amendments.

Trametinib+dabrafenib versus dabrafenib monotherapy

Using the company's pooled dataset and the ERG's remodelled OS only, the company's base case ICER increases from £104,069 per QALY gained to £150,821 per QALY gained. The size of the ICER increases further to £202,674 per QALY gained when the ERG's three amendments to costs and utility values are also implemented. When all of the ERG's changes are made, including the use of the OS data from the COMBI-d trial only, the ICER increases to £238,277 per QALY gained.

Trametinib+dabrafenib versus vemurafenib monotherapy

Using the company's pooled dataset and the ERG's remodelled OS only, the company's base case ICER increases from £94,436 per QALY gained to £137,373 per QALY gained. The size of the ICER increases further to £188,956 per QALY gained when the ERG's three amendments to costs and utility values are also implemented. When all of the ERG's changes are made, including the use of the OS data from the COMBI-d trial only, the ICER increases to £220,068 per QALY gained.

All of the ERG's revised ICERs are based on list prices.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Key points from the description of the underlying health problem (unresectable or metastatic melanoma) presented in the company submission[1] (CS) are reproduced (as bulleted items) by the Evidence Review Group (ERG) in Box 1. The ERG considers that these key points appropriately summarise the issues.

Box 1 Company's overview of unresectable or metastatic melanoma

Incidence and prevalence

- 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
- Approximately 45-50% of melanomas carry a mutation in the gene encoding BRAF, a critical component in the mitogen-activated protein kinase (MAPK) pathway which regulates normal cell growth, differentiation and survival
- The incidence of melanoma has been rising steadily in western populations over several decades[2] and incidence rates in the UK alone have at least quadrupled over the last 30 years Malignant melanoma is currently the fifth most common cancer in the UK, accounting for 4% of all new cancer cases. In 2013, 12,246 new cases of malignant melanoma were diagnosed in England and nearly 2,000 people died from the disease, representing 1% of all cancer deaths and 80% of deaths from skin cancer[3]
- Melanoma disproportionately affects a younger population than other cancers, resulting in a significant impact for patients, family and wider society. Approximately 27% of cases in the UK between 2009 and 2011 were in patients aged younger 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]

Staging

- The American Joint Commission on Cancer[4] (AJCC) system categorises melanoma into four stages. Stages I and II tumours are localised without regional or metastatic spread and can be cured by surgical resection. Melanoma may spread to nearby lymph nodes (stage III) or to other parts of the body (stage IV). Stage IV disease is sub-divided into three 'M' categories based on site(s) of metastases and serum levels of lactate dehydrogenase (LDH):
  - M1a - metastases in the skin, subcutaneous tissue or distant lymph nodes and normal LDH
  - M1b - metastases to the lung and normal LDH
  - M1c - metastases to any other visceral sites and normal LDH, or patients with metastases at any location but with an elevated LDH level.

Symptoms

- Patients with metastatic melanoma experience disease-related symptoms and health issues, including pain, fatigue, shortness of breath, sleeping problems, headaches, appetite loss, stomach cramps, and blood in stools. In addition, they will likely experience adverse effects related to their treatment.[5,6]

Prognosis

- The outlook for stage III melanoma patients is highly variable depending on nodal involvement; 5-year survival rates are in the region of 40% for patients with unresectable stage IIIc disease.[4] Historically, median survival times after stage IV diagnosis ranged from 6 to 12 months depending on the organs involved, but these are improving with the advent of new targeted and immunotherapies.[7,8] 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.[8] This is a particular concern given the marked propensity of melanoma to metastasise to the brain.[9]

2.2 Critique of company's overview of current service provision

2.2.1 Historical context

The company (CS, p36) provides an important commentary on the history of the treatment of patients with BRAF V600 mutation-positive advanced (unresectable or metastatic) melanoma. This information is presented in Box 2.

Box 2 Company's background to melanoma treatment

The past 5 years have 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. 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.

The ERG agrees that treatment options for patients with unresectable or metastatic BRAF V600 mutation-positive melanoma have advanced within the last 5 years and considers that the rapidity of the advance is of key importance to the present appraisal. Table 1 lists the treatment options recommended by NICE[10-15] since 2012. The ERG notes that in addition to BRAF inhibitors, ipilimumab and pembrolizumab immunotherapies are treatment options for all patients, irrespective of BRAF status. More recently, NICE has issued a FAD recommending the use of a third immunotherapy, nivolumab (February 2016).

Table 1 Treatment options available for the treatment of unresectable or metastatic melanoma since 2012

Treatment option	Treatment type	Patient population	Year recommended by NICE
Vemurafenib	BRAF inhibitor 4 tablets twice daily	BRAF V600 mutation-positive unresectable or metastatic melanoma	December 2012[11]
Dabrafenib	BRAF inhibitor 2 tablets twice daily	BRAF V600 mutation-positive unresectable or metastatic melanoma	October 2014[12]
Ipilimumab	Immunotherapy 3mg/kg intravenous every 3 weeks	All patients with unresectable or metastatic melanoma	December 2012 (previously treated patients)[13] July 2014 (treatment naïve patients)[10]
Pembrolizumab	PD-1 antibody 2mg/kg intravenous every 3 weeks	All patients with unresectable or metastatic melanoma	September 2015 (second-line, following treatment with ipilimumab)[14] November 2015 (first-line, prior to treatment with ipilimumab)[15]
Nivolumab	PD-1 antibody 3mg/kg intravenous every 2 weeks	All patients with unresectable or metastatic melanoma	Final appraisal determination issued in January 2016.[16]

There are currently two main options available to patients with BRAF mutation-positive melanoma: BRAF inhibitors (vemurafenib and dabrafenib) and immunotherapy (ipilimumab and pembrolizumab).

The ERG is aware that the majority of patients treated with a BRAF inhibitor achieve a rapid response; however, the response is often short-lived (approximately 6 months).[17] Response to treatment with ipilimumab may be more durable (survival rates plateau after 2 to 3 years although survival up to 5 years is reported);[17] however, it takes time for a response to be achieved and the proportion of patients who benefit is limited (10%).[18] Pembrolizumab has fewer side effects than ipilimumab and appears to benefit more patients (30 to 40%);[19] however, the data from the clinical trials in which pembrolizumab is compared with ipilimumab[19] and chemotherapy[20] are relatively immature and the long-term outcomes for patients treated with pembrolizumab are unclear at present. Clinical advice to the ERG is that patients with a BRAF mutation are offered, sequentially, both a BRAF inhibitor and immunotherapy. This is a changing field in that the lead immunotherapy treatment available to all patients up until the last quarter of 2015 was ipilimumab; however, pembrolizumab is now also an option.[15]

All of the available treatments can be used at any point in the disease pathway; however, the optimal sequencing of the available treatments is not yet established. A key issue is whether to use a BRAF inhibitor or immunotherapy for initial treatment in patients with BRAF

mutation-positive melanoma.[21] Clinical advice to the ERG is that conventional oncological practice leans towards prioritising treatments with the highest response rate, i.e. using BRAF inhibitor monotherapy before ipilimumab. However, for selected patients with low volume disease, it has been rational to consider prioritising ipilimumab with its slower kinetics of benefit but with a potential to deliver long-term disease control and survival, reserving BRAF therapy for salvage. Importantly this remains a matter of individual discussion and decision as the optimal sequencing of the available treatments is unclear. The introduction of pembrolizumab, and potentially nivolumab and combination BRAF and MEK directed therapy significantly impacts the treatment decision.

2.2.2 Company's overview of current service provision

The company presents a treatment algorithm (Figure 1) for metastatic melanoma. The algorithm is based on treatments appraised and recommended by NICE at the time that the CS was prepared (December 2015). The company states (CS, p37) that the use of trametinib+dabrafenib is likely to replace the use of the BRAF inhibitor monotherapies that are currently recommended by NICE.

Figure 1 shows pembrolizumab as a treatment option after treatment with ipilimumab (NICE guidance published on 7th October 2015). The ERG notes that NICE has recently recommended pembrolizumab[15] as a first-line treatment option (25th November 2015). Pembrolizumab is licensed for the treatment of patients with advanced (unresectable or metastatic) melanoma irrespective of BRAF V600 mutation status.

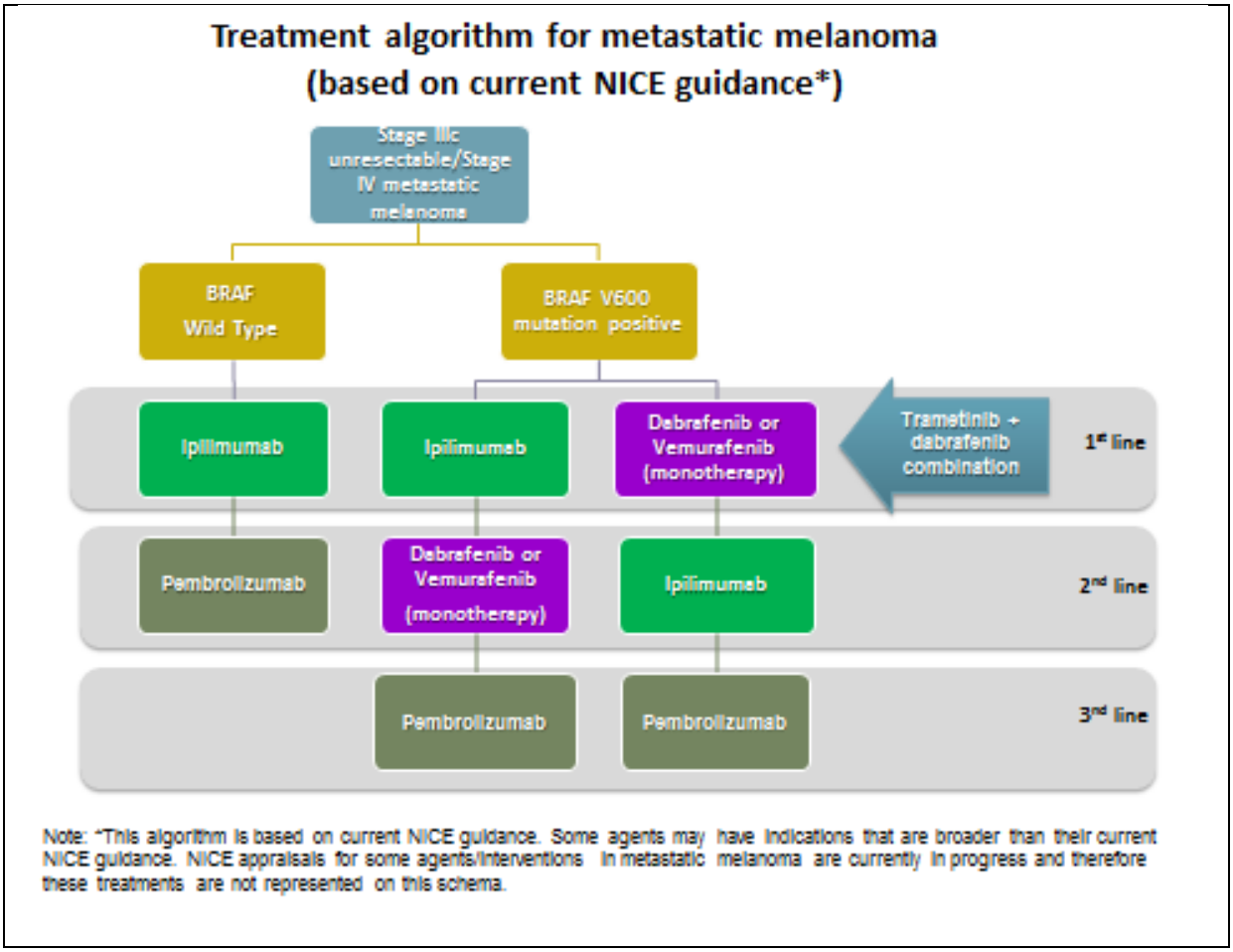

Figure 1 Treatment algorithm for metastatic melanoma

Source: CS, Figure 2

The ERG has reproduced (as bulleted items) the key points from the company's description of treatment options for patients with advanced (unresectable or metastatic) BRAF V600 melanoma in Box 3. The ERG considers the company's description to be accurate at the time the CS was written, with the caveat that the ERG is concerned that ipilimumab and pembrolizumab are not specified as comparators for this appraisal by NICE as they have been considered as comparators in previous appraisals and, consequently, they are not considered by the company (see discussion in later paragraphs of this section).

Box 3 Company's overview of current treatment options

Current treatment options and the place of trametinib+dabrafenib

- According to current NICE guidance, patients identified as having BRAF V600 mutation-positive tumours are eligible to receive treatment with a BRAF V600 inhibitor, either dabrafenib or vemurafenib. Ipilimumab is also recommended for previously untreated unresectable or metastatic melanoma (without regard for BRAF V600 status). A BRAF V600 inhibitor may be more likely chosen as the first-line option in patients with BRAF V600-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[22]
- The combination of trametinib+dabrafenib 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 V600 inhibition. **In the context of a positive NICE recommendation, the combination therapy would largely replace the use of BRAF V600 inhibitor monotherapies**

Issues relating to current clinical practice

- 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
- There are no prospective data from clinical trials that have established the optimal sequencing of a BRAF inhibitor and immunotherapy
- 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[23]
- Newer immunotherapeutic agents (nivolumab[24] and pembrolizumab[25]) have been licensed for the treatment of advanced melanoma in the past 6 months. **A Final Appraisal Determination (FAD) has recently been issued by NICE recommending pembrolizumab for advanced melanoma that has not previously been treated with ipilimumab (i.e. without regard for BRAF status). 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.**
- 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.

The company cites the results of its own market research.[23] The results of the research indicate that, in UK clinical practice, over 70% of patients with unresectable or metastatic BRAF V600 mutation-positive melanoma are treated at first-line with a BRAF inhibitor and less than 5% of patients receive treatment with ipilimumab at first-line. The remaining 25% are treated with chemotherapy, best supportive care or trametinib+dabrafenib (via patient access scheme or clinical trial). The ERG cautions that the company's data are based on very small numbers of patients (i.e. less than 30) and the research was conducted in March 2015, before NICE's positive recommendation[15] for pembrolizumab.

The company states that patients with rapidly progressing disease are likely to be treated initially with a BRAF inhibitor. Clinical advice to the ERG suggests that for patients with a life

expectancy of less than 3 months, initial therapy is always a BRAF inhibitor. In some cases this is the only treatment patients receive but in other cases this treatment will deliver sufficient benefit so as to allow patients to receive immunotherapy. Patients expected to live for more than 3 months are sometimes prescribed an immunotherapy; in the past this would have been ipilimumab, however, pembrolizumab is now likely to be the treatment of choice as it has recently been recommended by NICE.

The company emphasises that pembrolizumab is not a relevant comparator in this appraisal; the company's argument is that NICE's Final Appraisal Determination[15] document for the use of pembrolizumab as a first-line treatment was published too recently (in relation to the writing of the CS) for pembrolizumab to be in used in routine clinical practice in the NHS. The ERG agrees that NICE's positive recommendation for pembrolizumab as a first-line treatment coincided with the date of the company's submission to NICE for the present appraisal. However, the ERG considers that the introduction of pembrolizumab into the NHS is currently changing the treatment pathway for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma and is a relevant comparator in this appraisal. Pembrolizumab is likely to displace the use of ipilimumab and, in some cases, may also displace the use of BRAF inhibitors.

Ipilimumab was not specified as a relevant comparator to trametinib+dabrafenib in the NICE scope for this appraisal. The ERG notes that in the two appraisals of pembrolizumab, ipilimumab was considered a relevant comparator (in addition to vemurafenib and dabrafenib monotherapies).[14,15] Moreover, dabrafenib was a specified comparator in the appraisal of ipilimumab for previously treated melanoma,[10] and both ipilimumab and vemurafenib were specified as comparators in the appraisal of first-line treatment with dabrafenib.[12] The appraisal of nivolumab[26] includes dabrafenib, vemurafenib and ipilimumab as comparators, whilst the suspended appraisal of cobimetinib in combination vemurafenib[27] specifies only dabrafenib and vemurafenib. The ERG accepts that ipilimumab was not considered as a comparator in the appraisal under discussion; however, the rationale for the decision is unclear.

2.3 Number of patients in England eligible for treatment

In the CS, the company estimates that a maximum of 992 patients per annum would be eligible for treatment with trametinib+dabrafenib in England (

Table 2). The ERG notes that, in the published literature, estimates of the proportions of patients with tumours that harbour a BRAF mutation range from the 45% cited in the CS to

between 50% and 60%.[18,28,29] Overall, the ERG agrees that approximately 1000 patients per annum are likely to be eligible for treatment with trametinib+dabrafenib.

Table 2 Company's estimated number of patients eligible to receive trametinib+dabrafenib in England

	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[30]
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[28]
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[23] (ii) Biotrends Research Group. Treatment Trends: Melanoma (EU5). UK data set. November 2013[31]
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[23]
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
Source: CS, Table 8

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The decision problem described by the company in the CS is presented in Table 3. It relates to the final scope issued by NICE. Each parameter is discussed in more detail in the text following the table.

Table 3 NICE scope and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company's submission
Population	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma
Intervention	Trametinib+dabrafenib	Trametinib in combination with dabrafenib
Comparator(s)	• Dabrafenib • Vemurafenib	• Dabrafenib • Vemurafenib
Outcomes	The outcome measures to be considered include: • PFS • OS • ORR • AEs • HRQoL	The outcome measures considered include: • PFS • OS • RR • AEs • HRQoL
Economic analysis	The Reference Case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY 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 comparator technologies should be taken into account	The economic analysis estimated pairwise and incremental cost-effectiveness of trametinib+dabrafenib combination versus dabrafenib monotherapy and vemurafenib from the perspective of the NHS The DH agreed PAS prices are taken into account in the PAS addendum. The model horizon is 30 years, approximating a patient's lifetime
Subgroups to be considered	If evidence allows, consideration should be given to trametinib+dabrafenib as a first-line therapy or after treatment with immunotherapy	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 this combination

AE=adverse event; DH=Department of Health; HRQoL=health related quality of life; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; PSS=Personal Social Services; QALY=quality adjusted life year; RR=response rate; Source: CS, adapted from Table 1

3.1 Population

The treatment combination of trametinib+dabrafenib is licensed[32] for use in adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The NICE scope

and the company decision problem specify that the patient population is adults with unresectable or metastatic BRAF V600 mutation-positive melanoma.

The ERG notes that no particular treatment line is specified in either the licence[32] or in the final NICE scope. However, the patient populations recruited to the two pivotal trials that underpin the clinical effectiveness evidence presented in the CS (COMBI-d[33] and COMBI-v[34] trials) are described as being previously untreated. The only explicit mention of line of treatment for the trametinib+dabrafenib combination is in the Summary of Product Characteristics (SmPC)[35,36] where it is stated that other treatment options could be considered before treatment with the combination in this prior BRAF inhibitor treated population and that sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.

The ERG cautions that the inclusion and exclusion criteria for the COMBI-d and COMBI-v trials meant that only patients with an Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0 or 1 and patients without brain metastases were recruited. There is, therefore, no clinical evidence to support the use of trametinib+dabrafenib in patients with an ECOG PS of 2 or higher, or for patients with brain metastases. Clinical advice to the ERG is that patients with an ECOG PS of 2 or higher and patients with brain metastases are treated in UK clinical practice. The SmPC[35,36] explicitly states that the clinical effectiveness of trametinib+dabrafenib in people with brain metastases is currently unknown.

The findings from the COMBI-d and COMBI-v trials are only relevant to the cohort of patients in clinical practice with BRAF mutation-positive disease who have an ECOG PS 0-1 and no brain metastases. It is stated in the final NICE scope that some of these patients could have been treated with an immunotherapy instead of a BRAF inhibitor. It is not known whether trametinib+dabrafenib is more effective than an immunotherapy in this group of patients as there are no data available to allow this comparison to be undertaken.

3.2 Intervention

The intervention discussed in the CS is trametinib+dabrafenib and matches the intervention specified in the NICE scope.

Dabrafenib is an orally bioavailable and selective inhibitor of BRAF V600 kinase activity.[35] Trametinib is an orally bioavailable and selective inhibitor of the mitogen-activated protein kinase (MAPK) kinases MEK1 and MEK2, the additional key components of the MAPK pathway which sit downstream of BRAF.[36] The company states (CS, p37) that combining trametinib+dabrafenib provides concomitant inhibition of the MAPK pathway by

simultaneously targeting two discrete kinases, with the effect of delaying the development of resistance that is characteristic of treatment with a BRAF inhibitor monotherapy. An additional benefit of the treatment combination is a reduction in hyperproliferative skin toxicity compared with BRAF inhibitor monotherapy.

Trametinib is available in the UK as 0.5mg and 2mg film-coated tablets. The recommended dose is 2mg once daily.[36] Dabrafenib is available as 50mg and 75mg hard capsules. The recommended dose of dabrafenib, when used in combination with trametinib, is 150mg twice daily.[36] Before taking trametinib+dabrafenib, patients must have confirmation of a BRAF V600 positive mutation using a validated test.[36] The company states (CS, p25) that in England, BRAF testing is standard of care in clinical practice and that BRAF testing is available across the NHS in England.

In the CS (CS, p17) it is stated that trametinib and dabrafenib are both licensed as monotherapies but that there is no repackaging or reformulation specific to the treatment combination. The ERG notes that whilst dabrafenib monotherapy is recommended as a treatment option by NICE,[12] trametinib monotherapy has not been appraised by NICE.

3.3 Comparators

The comparators discussed in the CS are dabrafenib monotherapy and vemurafenib monotherapy and these match the comparators specified in the final NICE scope. The CS presents direct evidence from two key RCTs, one comparing trametinib+dabrafenib with dabrafenib+placebo (COMBI-d), the other comparing trametinib+dabrafenib with vemurafenib (COMBI-v).

The ERG notes that ipilimumab and pembrolizumab were not specified as comparators in the NICE scope. The ERG has discussed the implications of the omission of ipilimumab and pembrolizumab in Section 2.2.2 of this ERG report. In summary, the ERG considers that the rationale is not clear for not including ipilimumab and pembrolizumab to be relevant comparators to trametinib+dabrafenib in this appraisal for patients with BRAF mutation-positive melanoma who are relatively well and whose disease is not progressing.

3.4 Outcomes

Clinical evidence is reported in the CS for all five outcomes specified in the NICE scope: progression-free survival (PFS), overall survival (OS), response rate (reported as overall response rate [ORR] and duration of response), adverse events (AEs) of treatment and health related quality of life (HRQoL).

The ERG notes that, on the recommendation of the Independent Data Monitoring Committee (IDMC), the COMBI-v trial was stopped early for benefit, allowing patients from the vemurafenib arm of the trial with disease progression to cross over to treatment with trametinib+dabrafenib. In the CS (p17), the company states that, as a consequence of the early stopping rule, the interim OS analysis became the final OS analysis. The ERG was initially concerned that the COMBI-v trial had been stopped early for benefit as previous technology appraisals[37,38] have highlighted the fact that early closure of cancer trials can lead to exaggerated treatment effects that are not always borne out in the longer term.[39,40] However, after assessing the updated OS and PFS results from the March 2015 data cut, the ERG considers that, on this occasion, stopping the trial early does not appear to have biased the efficacy results in any way. The OS data are now very mature and are consistent with the findings from the April 2014 data cut (follow-up duration of 11 months in the trametinib+dabrafenib arm and 10 months in the vemurafenib arm).

The ERG notes that in its economic analysis, the company has pooled the individual patient data (IPD) for OS and PFS for the comparator and the intervention arms of the COMBI-d and COMBI-v trials. The company's stated rationale (CS, p186) is that combining the data from the two trials increases the sample size for each outcome and, consequently, the precision of the area under the curve (AUC) is also increased. The company states that AUC precision is particularly important for this appraisal as survival estimates have been shown to be the key drivers of cost effectiveness in previous melanoma appraisals.[10-15] However, whether pooling the IPD is appropriate methodology to adopt is uncertain. The ERG considers that results from a high quality blinded and placebo controlled trial (COMBI-d) are more likely to show the true effectiveness of a drug than results from an unblinded, non-placebo controlled trial (COMBI-v), or results generated from pooling data from a blinded and placebo controlled trial with those from an unblinded, non-placebo controlled trial.

As specified in the final NICE scope, the cost effectiveness of treatments was expressed in terms of incremental cost per quality adjusted life years (QALYs) gained. Outcomes were assessed over a 30-year time horizon (equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

3.5 Subgroups

The NICE scope states that if evidence allows, consideration should be given to trametinib+dabrafenib as a first-line therapy or after treatment with immunotherapy. The company states (CS, p9) that the clinical evidence presented in the CS relates almost entirely to the use of trametinib+dabrafenib as a first-line therapy. The ERG agrees with the

company that there is no clinical evidence available in the CS that allows consideration of trametinib+dabrafenib as a second-line treatment following treatment with immunotherapy.

3.6 Other considerations

The company did not identify any equality issues. The ERG is aware that the company has submitted a Patient Access Scheme (PAS) to the Department of Health (DH). The PAS price for trametinib has been approved; however, the PAS price for dabrafenib in the combination therapy has not yet been approved. The list prices of trametinib+dabrafenib, vemurafenib and dabrafenib are used in all of the cost effectiveness analyses presented in the CS.

4 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company in support of the use of trametinib+dabrafenib for the treatment of patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma.

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify, report and (if appropriate) meta-analyse or indirectly compare any clinical studies of relevance to the appraisal under discussion. The states (CS, p44) that the objective of the systematic review was to evaluate the efficacy and safety of the combination of trametinib+dabrafenib compared with first-line or second-line treatments for patients with metastatic melanoma.

4.2 Searches

The ERG's critique of the company's search strategy is presented in Appendix 1 of the ERG report. The CS includes a clear description of the search strategies used to identify relevant studies to inform the clinical effectiveness analysis and the cost effectiveness analysis. Full details of the strategies used in each section are reported in Appendices 8.2 and 8.9 and in Sections 4.1 and 5.1 of the CS. The searches were well reported and reproducible.

The ERG's critique of the company's search strategy is presented in Appendix 1 of the ERG report. The ERG considers that the searches carried out by the company are of a good standard. The search terms accurately reflect the population and indication and the search filters are of adequate quality. It is possible that by not searching for non-RCT information, the company could have missed relevant clinical results. The ERG is confident that the company did not miss any relevant RCT results.

The cost effectiveness searches are of reasonable quality and the filters that were used are correct.

4.2.1 Eligibility criteria

The company used an appropriate methodology to identify relevant articles. Two reviewers independently assessed all of the citations for potential inclusion through two stages. The ERG considers that the company's eligibility criteria are relevant to the company's systematic review objectives (Table 4). The ERG considers the criteria to be consistent with the NICE scope. The ERG notes that company did not search for non-RCT evidence.

The ERG also notes that a range of interventions (in addition to trametinib+dabrafenib) were included in the company's search criteria. The company states (CS, p44) that this is in line

with the systematic review objectives, i.e. to evaluate the safety and clinical effectiveness of trametinib+dabrafenib compared with first- or second-line treatments. The company reports that, although the eligibility criteria include a range of interventions identified as being relevant to clinical practice, only data relating to the comparisons of trametinib+dabrafenib with dabrafenib and vemurafenib are relevant to the present appraisal and therefore only these data are reported in the CS. The ERG considers that the comparisons of trametinib+dabrafenib with dabrafenib and vemurafenib are relevant to the present appraisal; the CS does not include any indirect comparisons.

Table 4 Eligibility criteria used in the company's search strategy

	Inclusion criteria	Key exclusion criteria	Rationale for inclusion
Population	• Adults aged ≥18 years • Disease: patients with unresectable or metastatic malignant melanoma • First or second line of therapy for the metastatic stage	• Studies that included melanoma patients with varying disease stages, but did not provide sub-group data for patients with metastatic disease. • 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	• 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	• 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	• These comparators were selected to potentially enable both direct and indirect comparisons between the interventions of interest
Outcomes	• OS • PFS • ORR • HRQoL • AEs	• 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
Study design	• RCT	• Any other study design	RCTs are the gold standard of clinical evidence
Language restrictions	• English	• Any other language	Language restriction was not expected to limit results substantially and data was available in English language

AE=adverse event; HRQoL=health related quality of life; ORR=overall response rate; OS=overall survival; PFS=progression-free survival
Source: CS, adapted from Table 10

4.2.2 Risk of bias

The company conducted a risk of bias assessment of the included trials using criteria recommended by the Centre for Reviews and Dissemination at the University of York.[41] The ERG considers this to be appropriate.

4.3 Evidence synthesis

Two Phase III trials were included in the company's systematic review. The characteristics and results of the COMBI-d trial (trametinib+dabrafenib versus dabrafenib+placebo) and the COMBI-v trial (trametinib+dabrafenib versus vemurafenib) were appropriately presented narratively in the CS. Evidence from a supporting Phase II trial (BRF113220 Part C) was also presented narratively. The company did not conduct any meta-analyses or indirect treatment comparisons.

4.4 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.4.1 Identified studies in the systematic review

Three RCTs were included in the company's systematic review. Two Phase III studies were included, the COMBI-d trial where the comparator of interest was dabrafenib+placebo and the COMBI-v trial where the comparator of interest was vemurafenib monotherapy. The supportive BRF113220 (Part C) trial compared two doses of trametinib+dabrafenib with dabrafenib monotherapy. The ERG is not aware of any additional studies that should have been included as part of the evidence base describing the clinical effectiveness of trametinib+dabrafenib versus a BRAF inhibitor monotherapy.

4.4.2 Statistical approach adopted for the conduct and analysis of studies included in the systematic review

All of the trials included patients with advanced BRAF V600 mutation-positive melanoma. In the COMBI-d trial, the efficacy and safety of trametinib+dabrafenib was compared with dabrafenib+placebo. In the COMBI-v trial, the efficacy and safety of trametinib+dabrafenib was compared with vemurafenib monotherapy. A full description and critique of these two trials is presented in this section of the ERG report.

In the BRF113220 (Part C) trial, two doses of trametinib+dabrafenib were compared with dabrafenib monotherapy. Results from this trial are only included in Appendix 2 of this ERG report, as they are not used to inform the company's economic model. In addition, the ERG is of the opinion that the evidence from this trial is limited due to high levels of patient crossover and small sample size.

Information relevant to the statistical approach taken by the company for the conduct and analysis of the studies included in the systematic review has been taken from the clinical study reports[42-44] (CSR) (including the trial statistical analysis plans [TSAP]) and the trial protocols), and from the CS.

Trial populations

In the COMBI-d and COMBI-v trials, for the analysis of all primary and secondary outcomes, the intention-to-treat (ITT) population was used. All patients were analysed according to the treatment arm to which they were initially randomised, regardless of which treatment they actually received. 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.

Outline of analyses

The COMBI-d trial closed in January 2013 and over-enrolled patients by 24%. Outcome data presented in the CS are from the planned analyses that were conducted with cut off dates of August 2013 for the primary PFS analysis and interim OS analysis and January 2015 for the final analysis of OS. Follow-up is still ongoing for the collection of additional survival and safety data.

In the CS, the company states that, for the COMBI-v trial, an interim OS analysis was scheduled to take place in April 2014. In July 2014 the study's IDMC met to review the data and recommended stopping the study early due to the superior efficacy of the combination arm and therefore the interim analysis became the 'final' analysis. A subsequent protocol amendment (August 2014) permitted patients in the vemurafenib arm to crossover to receive trametinib+dabrafenib.

Efficacy outcomes

The definitions, and methods of analysis, for the primary and secondary efficacy outcomes from the COMBI-d and COMBI-v trials are listed in Table 5. The ERG is satisfied that all of the outcomes were pre-specified in the TSAP and that all of the outcomes were fully reported in the CSR.

Table 5 Analysis strategy for key efficacy endpoints

Endpoint	Definition	Statistical method
COMBI-d: primary outcome		
PFS	The interval between the date of randomisation and the earliest date of objective DP or death due to any cause as assessed by investigators according to RECIST v1.1 criteria	Estimated using the K-M method and treatment comparisons made using a stratified log-rank test (based on the two stratification factors: BRAF V600 mutation and baseline lactate dehydrogenase (LDH) levels)
COMBI-d: secondary outcomes		
OS	The interval between date of randomisation and date of death due to any cause	Estimated using the K-M method and treatment comparisons made using a stratified log-rank test (based on the two stratification factors: BRAF V600 mutation and baseline lactate dehydrogenase (LDH) levels)
ORR	The percentage of patients achieving either a confirmed CR or PR at any time (per RECIST criteria v1.1) All responses were confirmed by imaging at least 4 weeks after the first RECIST response	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
DoR	The time from the first documented evidence of CR or PR until the first documented sign of progression or death due to any cause, among those subjects who achieved a confirmed CR or PR	Duration of response (DoR) was summarised for subjects with a confirmed CR or PR and the median was calculated using K-M estimates
COMBI-v: primary outcome		
OS	The interval between date of randomisation and date of death due to any cause	Estimated using the K-M method and treatment comparisons made using a stratified log-rank test (based on the two stratification factors: BRAF V600 mutation and baseline LDH levels)
COMBI-v: secondary outcomes		
PFS	The interval between the date of randomisation and the earliest date of objective DP or death due to any cause, as assessed by investigators according to RECIST v1.1 criteria	Estimated using the K-M method and treatment comparisons made using a stratified log-rank test (based on the two stratification factors: BRAF V600 mutation and baseline LDH) levels)
ORR	The percentage of patients achieving either a confirmed CR or PR at any time (per RECIST criteria v1.1). All responses were confirmed with a scan at least 4 weeks after the first RECIST response	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 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
DoR	The time from the first documented evidence of CR or PR until the first documented sign of progression or death due to any cause, among those subjects who achieved a confirmed CR or PR	DoR was summarised for subjects with a confirmed CR or PR and the median was calculated using Kaplan Meier estimates

CI=confidence interval; CR=complete response; DoR= duration of response; GSK=GlaxoSmithKline; K-M=Kaplan-Meier; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; DP=disease progression. Source: CS, adapted from Tables 14 and 15

Stratification

In both trials, subjects were stratified for two baseline factors: BRAF V600 mutation (V600E or V600K) and baseline lactate dehydrogenase (LDH) levels (≤upper limit of normal or >upper limit of normal (ULN).

Censoring methods

The censoring methods used for PFS in the COMBI-d trial are as follows: 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 anti-cancer 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. For 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 known to be still alive at the time of the analysis, censoring was performed using the date of last known contact.

Subjects without any adequate post baseline tumour assessments were also censored at the date of randomisation. An adequate assessment was defined as an assessment where the investigator determined response was complete response (CR), partial response (PR), or stable disease (SD). The date of response at that assessment was used for censoring.

Subgroup analyses

In both trials, the company performed subgroup analyses for BRAF V600 mutation (V600E or V600K) and baseline LDH levels (≤ULN or >ULN). For the COMBI-d trial, additional pre-determined factors considered to be important prognostic determinants in melanoma were explored in a stepwise Cox regression model: age (continuous), gender (male or female), baseline ECOG PS (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). For the COMBI-v trial, a stepwise stratified Cox regression model analysed the effect of various pre-determined prognostic factors: gender (male or female), baseline ECOG PS (0 or 1), baseline disease stage (IIIcM0/IVM1a/IVM1b or IVM1c), number of disease sites at baseline (<3 or ≥3). Subgroup analyses, for OS and PFS, were also performed for a range of baseline characteristics as shown in Table 6.

Crossover adjustment methods

In the COMBI-d trial patients were not allowed to cross over.

In the COMBI-v trial, patients in the vemurafenib arm were allowed to cross over to the trametinib+dabrafenib arm after the study was stopped early. The School of Health and Related Research (ScHARR) in Sheffield undertook an extensive assessment to identify which methods would be the most appropriate for the analysis of the COMBI-v dataset. ScHARR investigated two possible methods that could be applied to the COMBI-v OS data: the Rank-Preserving Structural Failure Time Model (RPSFTM) and the Inverse Probability of Censoring Weighting (IPCW) methodology.

The RPSFTM uses a counterfactual framework to estimate what survival times would have been observed if treatment switching had not occurred. The standard one-parameter version of the method depends on the 'common treatment effect' assumption – i.e. patients who are originally randomised to the intervention group will experience the same treatment effect as patients who switch treatment. RPSFTM also assumes that the treatment groups will be balanced at randomisation so there are no differences between them other than the treatment allocations. The 'common treatment assumption' may be problematic if switching is only permitted after disease progression; for COMBI-v this is not an issue as only five out of 21 (6%) switching patients had experienced disease progression.

The RPSFTM can be performed under two different assumptions relating to the continuation of the treatment effect after treatment discontinuation. The first assumption is 'on treatment analyses' where it is assumed that patients can cross over from the control group to the intervention and also vice versa. This assumption offers an estimate of the treatment effect of full treatment compared to no treatment and presumes that the treatment effect is gone as soon as treatment is discontinued. The alternative assumption is 'treatment group analysis' where it is assumed that there is no crossover from the intervention to the control group and that, once treatment has begun, the patient remains in the 'treated' group. This approach estimates what the average effect of being randomised to the intervention group compared with the control group would be over the observed lifetime of the full patient population.

The IPCW method does not rely on the 'common treatment effect' assumption. Using this method patients are censored at the point of treatment switch and the remaining observations are adjusted based on baseline and time-dependent covariates, in order to adjust for any selection bias that may be caused by switching-related censoring. This method is based on the 'no unmeasured confounders' assumption, which means that all data relating to baseline and time-dependent patient characteristics that influence the

probability of treatment switch and the probability of death should be available. The IPCW method is prone to bias through a lack of available time-dependent data, resulting from data collection being interrupted for some covariates after the interim analysis stage.

The company states that the RPSFTM 'treatment group' approach was the most appropriate method for adjusting the OS data from the COMBI-v trial in order to produce an estimate of the treatment effect that would have been observed in the absence of treatment switching. The ERG agrees that the RPFSTM 'treatment group' approach was the correct method to choose and, as only 6% of patients switched over from the vemurafenib arm to the combination arm, the results prior to any crossover adjustment and the results including crossover adjustment do not differ greatly.

ERG assessment of statistical approach

A summary of the checks made by the ERG regarding the statistical approach adopted by the company to analyse data from the COMBI-d and COMBI-v trials is provided in Table 6.

Table 6 ERG assessment of statistical approaches used to analyse data from the COMBI-d and COMBI-v trials

Component	Statistical approach (COMBI-d)	ERG comments (COMBI-d)	Statistical approach (COMBI-v)	ERG comments (COMBI-v)
Sample size calculation	Provided in the CS (pages 76-77)	The ERG considers that the methods used to calculate the sample size are correct	Provided in the CS (pages 76-77)	The ERG considers that the methods used to calculate the sample size are correct
Protocol amendments	Provided in the CSR (Section 4.3)	The ERG notes that the changes detailed in the protocol amendments including updating the data analysis and statistical considerations section in light of over enrolling were unlikely to have been driven by the results of the trial and are therefore not a cause for concern. Most of the protocol amendments were carried out prior to the analysis being conducted. A protocol amendment was carried out post primary analysis being conducted but it does not affect the results in any way so is not a cause for concern	Provided in the CSR (Section 4.3)	The ERG notes that the changes detailed in the protocol amendments were unlikely to have been driven by the results of the trial and are therefore not a cause for concern. All protocol amendments were carried out prior to the analysis being conducted
Missing data approach	Provided in the CS (pages 82-83)	The ERG is satisfied that the company took a suitable approach to handling missing data	Provided in the CS (pages 82-83)	The ERG is satisfied that the company took a suitable approach to handling missing data
Subgroup analyses	For OS and PFS only (pre-planned): • BRAF V600 mutation (V600E or V600K) • Age (<65 years or ≥65 years) Gender (male versus female) For OS and PFS only (post-hoc): • 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	The ERG is satisfied that the results of all subgroup analyses are provided in the CSR	For OS and PFS only (pre-planned): • 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	The ERG is satisfied that the results of all subgroup analyses are provided in the CSR

Component	Statistical approach (COMBI-d)	ERG comments (COMBI-d)	Statistical approach (COMBI-v)	ERG comments (COMBI-v)
	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 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 versus female) and age (≥65 versus <65 years, and ≥ 75 versus <75 years)		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 (all pre-planned) were explored in the subgroup analysis of ORR Subgroup analyses of some safety data were undertaken by gender (male versus. female) and age (≥65 versus <65 years, and ≥ 75 versus <75 years)	
Adverse events	Safety was assessed through summaries of most common AEs, AEs by causality, SAEs, AEs of special interest and AEs leading to treatment discontinuation, dose interruptions or dose reductions	The ERG is satisfied that the results of all of the AE data analyses are provided in the CSR	Safety was assessed through summaries of most common AEs, AEs by causality, SAEs, AEs of special interest and AEs leading to treatment discontinuation, dose interruptions or dose reductions	The ERG is satisfied that the results of all the AE data analyses are provided in the CSR
Health-related quality of life	• EORTC-QLQ-C30 • EQ-5D questionnaire	The ERG is satisfied that the methodology used to analyse HRQoL data is appropriate	• EORTC-QLQ-C30 • EQ-5D questionnaire • Melanoma Subscale of the FACT-M questionnaire	The ERG is satisfied that the methodology used to analyse HRQoL data is appropriate

AE=Adverse Event; CS=company submission; CSR=clinical study report; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3; EQ-5D=EuroQol-5 Dimensions; ERG=Evidence Review Group; FACT-M=Functional Assessment of Cancer Therapy—Melanoma; HRQoL=health-related quality of life; LDH=lactate dehydrogenase; OS=overall survival; PFS=progression-free survival; SAE=Serious Adverse Event; ULN=upper limit of normal
Source: CS, adapted from Table 15, CSR and ERG comment

4.4.3 Characteristics of the studies included in the systematic review

Direct Phase III RCT evidence for the comparisons of trametinib+dabrafenib versus (i) dabrafenib+placebo and (ii) vemurafenib monotherapy was available. Data from the COMBI-d and COMBI-v trials were published in peer-reviewed journals,[33,34] with full appendices. The company also provided the CSRs for both trials.

Characteristics of the COMBI-d and COMBI-v trials

The key characteristics of the COMBI-d and COMBI-v trials are presented in Table 7. The COMBI-d trial was a double-blind, RCT of trametinib+dabrafenib versus dabrafenib+placebo in adult patients (aged ≥18 years) with previously untreated stage IIIc (unresectable) or stage IV (metastatic) BRAF V600 melanoma. It was conducted internationally and recruited 423 patients. There were ten UK centres (33 patients). The primary endpoint was investigator–assessed PFS.

The COMBI-v trial was an open-label RCT of trametinib+dabrafenib versus vemurafenib monotherapy in adult patients (aged ≥18 years) with previously untreated stage IIIc (unresectable) or stage IV (metastatic) BRAF V600 melanoma. It was conducted in Europe and recruited 704 patients. There were seven UK centres (39 patients). The primary endpoint was OS. The company states (CS, Table 14), that the COMBI-v trial was designed to be open-label due to the complexity involved in designing three matching placebo tablets (dabrafenib, trametinib and vemurafenib) and patients would have had to take multiple tablets. The ERG accepts that a placebo-controlled trial would have placed a burden on the patients. However, the ERG notes that the coBRIM trial[45,46] (cobimetinib+vemurafenib versus vemurafenib) was placebo-controlled. In addition, the ERG notes that the PFS outcome of the COMBI-v trial relies on investigator assessment with no independent central review procedures. The ERG considers that the PFS and response rate outcomes of the COMBI-v trial would be more robust if an independent central review of radiography had been in place.

Table 7 Key characteristics of the COMBI-d and COMBI-v trials

	COMBI-d	COMBI-v
Design	Double-blind, Phase III RCT	Open-label, Phase III RCT
Location	14 countries worldwide, 103 centres (10 UK centres, 33 patients)	28 countries across Europe (7 UK centres, 39 patients)
Intervention	Dabrafenib (150mg b.d.) Trametinib (2mg o.d.)	Dabrafenib (150mg b.d.) Trametinib (2mg o.d.)
Comparator	Dabrafenib (150mg b.d.) Placebo trametinib (o.d.)	Vemurafenib (960mg o.d.)
Patient population	N=423 Previously untreated stage IIIc (unresectable) or stage IV (metastatic) BRAF V600E/K mutation-positive melanoma	N=704 Previously untreated stage IIIc (unresectable) or stage IV (metastatic) BRAF V600E/K mutation-positive melanoma
Primary outcome	Investigator-assessed PFS	OS
Secondary outcomes	OS, ORR, duration of response, HRQoL, AEs	Investigator-assessed PFS, ORR, duration of response, HRQoL, AEs
Trial status	Ongoing. Enrolment commenced in May 2012 and closed in January 2013. Cut off for primary analysis for PFS: 26 August 2013. Cut off for final analysis of OS: 12 January 2015. 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. Cut off for updated analysis of OS: 13 March 2015. 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)

AE=adverse event; b.d=twice daily; CTCAE=Common Terminology Criteria for Adverse Events; ECOG=Eastern Co-operative Oncology Group; HRQoL=health-related quality of life; MEK=mitogen-activated protein kinase o.d=once daily; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PS=performance status; RCT=randomised controlled trial; RECIST=Response Evaluation Criteria in Solid Tumours
Source: CS, adapted from Table 14

Characteristics of patients in the COMBI-d and COMBI-v trials

The key baseline characteristics of the patients in the COMBI-d and COMBI-v trials are listed in Table 8. The ERG agrees with the company that patients in the COMBI-d trial are well-balanced across the treatment groups, with the exception of the proportions of patients with visceral disease (slightly higher in the trametinib+dabrafenib arm).

The ERG considers that the patients in the COMBI-v trial are also well balanced across the treatment groups, although there were (slightly) more patients in the vemurafenib arm who had received prior immunotherapy treatment. The company has emphasised that in both the COMBI-d and COMBI-v trials, all prior systemic therapy was administered in the neoadjuvant or adjuvant setting.

The ERG notes that the patients recruited to the COMBI-d and COMBI-v trials were limited to those with an ECOG PS of 0 or 1; an ECOG PS of 0 or 1 suggests that the patients in the trials were relatively well at the time of enrolment. The presence of brain metastases was also an exclusion factor in both trials. Clinical advice to the ERG is that patients with ECOG

PS of 2, 3 and 4 are treated in the NHS and patients with brain metastases are also treated in the NHS.

Table 8 Key characteristics of patients in the COMBI-d and COMBI-v trials

	COMBI-d		COMBI-v	
	Trametinib+ dabrafenib N=211[a]	**Dabrafenib+ placebo N=212[b]**	**Trametinib+ dabrafenib N=352**	**Vemurafenib N=352**
Age, years				
Mean (sd)	55.1 (13.33)	55.3 (13.75)	54.1 (13.83)	54.3 (14.06)
Sex				
% Male	53%	54%	59%	51%
ECOG PS				
ECOG 0	71%	71%	71%	70%
ECOG 1	29%	29%	29%	30%
BRAF mutation status				
V600E	85%	85%	90%	90
V600K	15%	14%	10%	10%
V600E & V600K	0	0	1%	<1%
Stage				
IVM1c	67%	65%	≥63%	59%
IIIc, IVM1a or IVM1b	33%	34%	37%	41%
M Stage at screening				
M0	2%	5%	4%	7%
M1a	9%	15%	16%	14%
M1b	21%	15%	17%	19%
M1c	67%	65%	63%	59%
LDH				
≤ULN	63%	66%	66%	68%
≥ULN	36%	33%	34%	32%
Visceral disease (lungs, heart, organs of the digestive, excretory, reproductive, and circulatory systems, not lymph nodes)				
No	22%	31%	21%	23%
Yes	78%	68%	79%	77%
Number disease sites (sites of disease based on unique RECIST target and non-target lesions)				
≥3	48%	43%	50%	43%
≤3	52%	56%	50%	57%
Prior anti-cancer therapy (patients may have received ≥1)				
Any	94%	97%	88%	90%
Prior immunotherapy (adjuvant setting**)**				
Yes	27%	29%	17%	26%
No	73%	71%	83%	74%

ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; sd=standard deviation; ULN=upper limit of normal
Source: CS, adapted from Table 23 and Table 24

4.4.4 Assessment of risk of bias of the studies included in the systematic review

The company conducted a risk of bias assessment for the COMBI-d and COMBI-v trials using the criteria recommended by the Centre for Reviews and Dissemination at the University of York.[41]

For the COMBI-d trial, the ERG agrees with the company's assessment (Table 9). For the COMBI-v trial, the ERG agrees with the majority of the company's assessment, but considers that, as randomisation was conducted centrally using an interactive voice response system (IVRS), the concealment of treatment allocation in the trial was adequate. The use of the IVRS ensures that a patient's allocation to a particular treatment arm could not be predicted or influenced.

The ERG notes that the COMBI-v trial was an open-label trial that did not include a blinded Independent Review Committee (BIRC) of investigator-assessed radiological outcomes. It is unclear to what extent the key outcomes of the trial may be biased (PFS, ORR and HRQoL).

The ERG notes that the COMBI-v trial was stopped early for benefit. The ERG was initially concerned that the COMBI-v trial had been stopped early for benefit as previous technology appraisals[37,38] have highlighted the fact that early closure of cancer trials may lead to exaggerated treatment effects that are not borne out in the longer term.[39,40] However, after assessing the updated OS and PFS results from the March 2015 data cut, the ERG considers that, on this occasion, stopping the trial early does not appear to have biased the efficacy results in any way. The OS data are now virtually mature and are consistent with the findings from the April 2014 data cut (follow-up duration of 11 months in the trametinib+dabrafenib arm and 10 months in the vemurafenib arm).

Table 9 Company assessment of risk of bias for the COMBI-d and COMBI-v trials (with ERG comments)

Risk of bias criteria	COMBI-d	ERG comment	COMBI-v	ERG comment
Was randomisation carried out appropriately?	Yes	Agree	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	Agree	Treatment allocation was not concealed as this was an open-label study	At the time of randomisation, treatment allocation was concealed. However, the trial was an open-label study, so patients were soon informed of their allocation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Agree	No	Agree
Were there any unexpected imbalances in drop-outs between groups?	No	Agree	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree	No	Agree
Did the analysis include an intention-to-treat analysis? Was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree	Yes	Agree

Source: CS, adapted from Table 26

4.5 Results from the studies included in the systematic review

4.6 Results from the COMBI-d trial

PFS, OS and ORR results for the August 2013 data analyses (primary PFS analysis) and the January 2015 analyses (final OS analysis) from the COMBI-d trial are reported in this section (Table 10).

4.6.1 Progression-free survival (primary outcome)

At the time of the August 2013 analysis, median PFS (investigator-assessed) was 9.3 months in the trametinib+dabrafenib arm and 8.8 months in the dabrafenib+placebo arm, a difference of 0.5 months. The risk reduction associated with trametinib+dabrafenib was 25%, hazard ratio (HR) 0.75, (95% CI: 0.57 to 0.99, p=0.035). The company (CS, p102) reports that the results of a pre-specified assessment of PFS carried out by a BIRC were consistent with the results of the investigator assessment. In the BIRC analysis median PFS was 10.1 months in the trametinib+dabrafenib arm and 9.5 months in the dabrafenib+placebo arm, a difference of 0.6 months. The risk reduction associated with trametinib+dabrafenib was 22% (HR=0.78, 95% CI: 0.59 to 1.04, p=0.085).

At the time of the January 2015 analysis, median PFS was 11 months in the trametinib+dabrafenib arm and 8.8 months in the dabrafenib+placebo arm, a difference of 2.2 months. The risk reduction associated with treatment with trametinib+dabrafenib was 33% (HR=0.67, 95% CI: 0.53 to 0.84, p=0.0004).

The company presents the Kaplan-Meier (K-M) curves for both the August 2013 and January 2015 PFS analyses (CS, Figures 10 and 11). The ERG considers that the August 2013 survival curves appear to be parallel over time with clear separation and then cross over around 11 months post-randomisation. As the company are using the Pike estimator to estimate the treatment effect it is not concerning that the survival curves are not parallel.

The K-M curves for PFS at January 2015 (CS, Figure 11) demonstrate that there is early separation of the curves at around 2 months post-randomisation and this separation continues into follow-up until 30 months post-randomisation.

The company states (CS, p102) that as the 2015 data analysis was not pre-planned and the p-values were not adjusted for multiple testing, three sensitivity analyses of PFS were carried out to demonstrate the robustness of the treatment effect: i) including symptomatic progression as an event; ii) considering the start of a new anti-cancer therapy or extended loss to follow-up as an event and iii) considering progression after the start of a new anti-cancer therapy or after extended loss to follow-up as an event. The ERG agrees with the company's conclusion that the results of each of the sensitivity analyses (CS, Table 28) are consistent with the results reported in the August 2013 PFS analysis.

4.6.2 Overall survival

At the time of the final OS analysis (January 2015), median OS was 25.1 months in the trametinib+dabrafenib arm and 18.7 months in the dabrafenib+placebo arm, a difference of 6.4 months. The difference represents a risk reduction associated with trametinib+dabrafenib of 29% (HR=0.71, 95% CI: 0.55 to 0.92, p=0.0107).

The K-M curves for OS at January 2015 (CS, Figure 12) demonstrate that there is early separation of the curves at around 2 months post-randomisation and this separation continues into follow-up until 34 months.

The company states (CS, p106) that the OS benefit for patients in the trametinib+dabrafenib arm persisted even though a greater proportion of patients in the dabrafenib+placebo arm received anti-cancer treatment when their disease progressed (33% versus 53% respectively). The ERG notes from Table 30 of the CS that the majority of patients were treated with ipilimumab following disease progression.

4.6.3 Overall response rate

The ORR was higher in the trametinib+dabrafenib arm than in the dabrafenib+placebo arm at the August 2013 and the January 2015 data cuts. The ERG notes that the percentage of patients in each arm with a response was similar at both time points (67% versus 51% and 69% versus 53%) for patients in the trametinib+dabrafenib and dabrafenib+placebo arms respectively.

The company reports (CS, p106) that the ORR results based on the BIRC review (August 2013) were similar to the ORR results calculated from the investigator-assessed data.

Table 10 Summary of efficacy findings from the COMBI-d trial

Endpoint	26th August 2013		12th January 2015	
	Trametinib+ dabrafenib N=211	Dabrafenib+ placebo N=212	Trametinib+ dabrafenib N=211	Dabrafenib+ placebo N=212
Investigator-assessed PFS – primary outcome				
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]				
Median (95% CI)	9.3 (7.7 to 11.1)	8.8 (5.9 to 10.9)	11.0 (8.0 to 13.9)	8.8 (5.9 to 9.3)
Adjusted HR estimate [b] (95% CI)	0.75 (0.57 to 0.99)		0.67 (0.53 to 0.84)	
Stratified log rank p-value[b]	0.035		0.0004	
OS				
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 OS (months)[a]				
Median (95% CI)	NR (14.1 to NR)	NR (NR to NR)	25.1 (19.2 to NR)	18.7 (15.2 to 23.7)
Adjusted HR estimate[b] (95% CI)	0.63 (0.42 to 0.94)		0.71 (0.55 to 0.92)	
Stratified log rank p-value[b]	p=0.023		0.0107	
Estimates for OS at 1 year and 2 years (%)				
1 year (95% CI)	NA	NA	74% (67 to 79)	68% (61 to 74)
2 year (95% CI)	NA	NA	51% (44 to 58)	42% (35 to 49)
ORR				
CR+PR, n (%) 95% CI	140 (67) (59.9 to 73.0)	108 (51) (44.5 to 58.4)	144 (69) (61.8 to 74.8)	112 (53) (46.3 to 60.2)
p-value[c]	p=0.0015		p=0.0014	
Duration of response Median, months (95% CI)	9.2 (7.4 to NR)	10.2 (7.5 to NR)	12.9 (9.4 to 19.5)	10.6 (9.1 to 13.8)

a. Quartiles were estimated using the Brookmeyer Crowley method.

b. Hazard ratios are estimated using a Pike estimator. Hazard ratio and p-value from stratified log-rank test are adjusted for randomised strata: baseline LDH and BRAF mutation status

c Chi-squared test was used to calculate the p-value

CR=complete response; HR=hazard ratio; NR=not reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response

Source: CS, adapted from Table 3, Table 27, Table 29, Table 31

4.6.4 Health-related quality of life

The HRQoL data presented in the CS (CS, Section 4.7.1.3, p107-111) are those that result from analyses of data from the 26 August 2013 data cut of the COMBI-d trial. The company reports that results from analysing data from the January 2015 data cut are similar to, and

consistent with, those resulting from analyses of data from the earlier data cut. Results are presented from analyses of data collected using three tools: the European Organisation for Research and Treatment of Cancer Quality of Life C-30 Questionnaire[47] (EORTC-QLQ-30), the EuroQol Visual Analogue Scale (EQ VAS) and the Euroqol-5 Dimensions (EQ-5D) questionnaire.[48] Data were collected at baseline weeks 8, 16, 24, 32, 40 and at disease progression.

The EORTC-QLQ-C30 questionnaire comprises a measure of global health status, five functional dimensions (physical, social, role, emotional, and cognitive functioning) and nine symptom domains (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). Rates of completion, as a percentage of available patients, were high in both treatment arms (>90% at baseline, weeks 8, 16, 24, 32 and 40, and >70% at disease progression).

The company reports that, overall HRQoL, as measured by the EORTC-QLQ-30 global health status score, was shown to be 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+placebo. The majority of the EORTC-QLQ-30 functional scores tended to favour treatment with trametinib+dabrafenib compared with dabrafenib+placebo, the exceptions being cognitive functioning at weeks 16, 24, 32 and at progression. The ERG, however, notes that the confidence intervals for all functional scores are wide and only a few are either clinically meaningful or statistically significant. Results for the EORTC-QLQ-30 symptom domain scores were mixed, with some scores being better for the trametinib+dabrafenib cohort and others better for those treated with dabrafenib+placebo. At all reported time points, the pain and insomnia scores for patients treated with trametinib+dabrafenib were statistically significantly ($p>0.05$) better than those for the dabrafenib+placebo cohort. The ERG notes that, again, confidence intervals were wide and only a minority of the scores were either clinically or statistically significant.

EQ VAS scores were similar at baseline for both treatment groups (71.7 for patients treated with trametinib+dabrafenib and 70.3 for dabrafenib monotherapy patients). The only time point at which there was a statistically significant difference in results between treatment arms was at week 40. At this point, results favoured treatment with trametinib+dabrafenib.

Utility scores, calculated from data collected using the EQ-5D questionnaire, were shown to be comparable between the treatment arms at baseline (0.765 and 0.730 for the combination therapy and dabrafenib+placebo, respectively).[43] The only time point at which

there was a statistically significant difference in results between treatment arms was at week 16. At this point, results favoured treatment with trametinib+dabrafenib rather than dabrafenib monotherapy.

The results from the analyses of HRQoL data collected during the COMBI-d trial are mixed. On balance, the EORTC-QLQ-30 scores suggest that treatment with trametinib+dabrafenib may result in limited improvement in HRQoL compared with dabrafenib monotherapy. However, confidence intervals are wide, which raises uncertainty around the precision of the differences. Furthermore, results from the analyses of EQ VAS and EQ-5D questionnaire data show that, except for two occasions (week 40 results from the analysis of EQ VAS data and week 16 results from the analysis of EQ-5D questionnaire data), the differences in mean scores between those in the cohort of patients treated with trametinib+dabrafenib and those treated with dabrafenib+placebo are not statistically significantly different.

4.7 Results from the COMBI-v trial

PFS, OS and ORR results for the April 2014 data analyses (interim and subsequent final OS analysis) and the updated March 2015 data cut from the COMBI-v trial are reported in this section (Table 11).

4.7.1 Overall survival

At the April 2014 interim analysis (median follow-up of 11 months), median OS in the trametinib+dabrafenib arm had not been reached and OS in the vemurafenib monotherapy arm was 17.2 months. The risk reduction associated with trametinib+dabrafenib was 31% (HR=0.69, 95% CI: 0.53 to 0.0.89, p=0.005).

At the March 2015 analysis (median follow-up of 19 months), median OS in the trametinib+dabrafenib arm was 25.6 months compared with 18 months in the vemurafenib monotherapy arm, a difference of 7.6 months. The risk reduction associated with treatment with trametinib+dabrafenib was 34% (HR=0.66, 95% CI: 0.53 to 0.0.81, p<0.001).

The company states (CS, p113) that after the COMBI-v trial was stopped early for benefit in July 2014, 6% (21/352) of patients from the vemurafenib arm began treatment with trametinib+dabrafenib; five of these patients had already progressed CS, p170). The company acknowledges that patients changing treatments may have impacted the results of the March 2015 OS analysis. The CS (CS, p125) therefore includes the results of an OS analysis that adjusts for patient crossover by using the RPSFTM. The ERG notes that the RPFSTM hazard ratio (HR=0.63, 95% CI: 0.50 to 0.79) is similar to that of the HR for the ITT population (HR=0.66, 95% CI: 0.53 to 0.81). The ERG agrees that the company has applied

the correct method to perform the crossover adjustment and the results demonstrate that, as only 6% of patients crossed over, there was very little impact on the results.

The company presents the K-M curve for the March 2015 OS data cut for the COMBI-v trial (CS, Figure 14). The ERG agrees with the company that there is early separation of the curves and this separation continues into follow-up.

The company reports (CS, p113) that a greater proportion of patients in the dabrafenib+placebo arm compared with the trametinib+dabrafenib arm received anti-cancer treatment when their disease progressed (51% versus 34% respectively). The ERG notes from Table 36 of the CS that the majority of patients were treated with ipilimumab following disease progression.

4.7.2 Progression-free survival

At the April 2013 analysis of the COMBI-v trial (follow-up of 11 months), median PFS (investigator-assessed) was 11.4 months in the trametinib+dabrafenib arm and 7.3 months in the vemurafenib monotherapy arm, a difference of 4.1 months. The risk reduction associated with trametinib+dabrafenib was 44% (HR=0.56, 95% CI: 0.46 to 0.69, p<0.001).

At the March 2015 data cut, median PFS was 12.6 months in the trametinib+dabrafenib arm and 7.3 months in the vemurafenib monotherapy arm, a difference of 5.3 months. The risk reduction associated with trametinib+dabrafenib was 39% (HR=0.61, 95% CI: 0.51 to 0.73, p<0.001). The company (CS, p102) emphasises that the 2015 data analysis was not pre-planned and that the p-value was not adjusted for multiple testing.

The company conducted five sensitivity analyses of PFS, namely: i) symptomatic progressions determined by the investigator; ii) considering start of new anti-cancer therapy as an event; iii) considering radiological progression after extended loss to follow-up or start of new anti-cancer therapy as an event; iv) Cox regression proportional hazards regression model and v) using derived responses from investigator lesion assessments. The ERG agrees with the company's conclusion that the results of the sensitivity analyses for PFS were consistent with the results of the ITT analysis with HRs in the range of 0.53 to 0.57.

The ERG notes that the COMBI-v trial did not include a blinded assessment of PFS by an Independent Review Committee.

The company presents the K-M curves for the March 2015 PFS analyses (CS, Figure 15). The ERG considers that there is early separation of the curves that continues into follow-up.

4.7.3 Overall response rate

The ORR was higher in the trametinib+dabrafenib arm than in the vemurafenib monotherapy arm of the COMBI-v trial at April 2014 and at March 2015. The ERG notes that the percentage of patients in each arm with a response was similar at both time points, 64% versus 51% and 66% versus 53% in the trametinib+dabrafenib and vemurafenib arms respectively.

Table 11 Summary of efficacy findings from the COMBI-v trial

Endpoint	17th April 2014		13th March 2015	
	Trametinib+ dabrafenib N=352	Vemurafenib monotherapy N=352	Trametinib+ dabrafenib N=352	Vemurafenib monotherapy N=352
OS – Primary outcome				
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 OS (months)[a]				
Median (95% CI)	NR (18.3 to NR)	17.2 (16.4 to NR)	25.6 (22.6 to NR)	18.0 (15.6 to 20.7)
Adjusted HR estimate[b] (95% CI)	0.69 (0.53 to 0.89)		0.66 (0.53 to 0.81)	
Stratified log rank p-value[b]	p=0.005		p<0.001	
Estimates for OS at 1 year and 2 years (%)				
1 year (95% CI)	72% (67 to 77)	NA	73% (68 to 77)	64% (59 to 69)
2 year (95% CI)	65% (59 to 70)	NA	51% (45 to 57)	38% (32 to 44)
Investigator-assessed PFS				
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]				
Median (95% CI)	11.4 (9.9 to 14.9)	7.3 (5.8 to 7.8)	12.6 (10.7 to 15.5)	7.3 (5.8 to 7.8)
Adjusted HR estimate [b] (95% CI)	0.56 (0.46 to 0.69)		0.61 (0.51 to 0.73)	
Stratified log rank p-value[b]	p<0.001		p<0.001	
ORR				
CR+PR, n (%) 95% CI	226 (64) (59.1 to 69.4)	180 (51) (46.1 to 56.8)	231 (66) (60.4 to 70.6)	186 (53) (47.5 to 58.2)
p-value[c]	p=0.0005		p=0.0008	
Duration of response Median, months (95% CI)	13.8 (11.0 to NR)	7.5 (7.3 to 9.3)	13.8 (11.2 to 18.1)	8.5 (7.4 to 9.7)

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

c Chi-squared test was used to calculate the p-value

NA=not available; NR=not reached

Source: CS, adapted from Table 36, Table 37, Table 38

4.7.4 Health-related quality of life

The HRQoL data presented in the CS (Section 4.7.2.3, p116-120) are those that result from analyses of data from the 17 April 2014 data cut of the COMBI-v trial. These data were collected using the EORTC QLQ-C30 questionnaire, the EQ VAS, the EQ-5D questionnaire and the Melanoma Subscale of the Functional Assessment of Cancer Therapy—Melanoma (FACT-M) questionnaire. Assessment points were baseline, weeks 8, 16, 24, 32, 40, 48 and on progression.

High proportions of patients, as a percentage of available patients, in both treatment arms completed the EORTC-QLQ-C30 questionnaires (>95% at baseline, >80% at all assessments until week 56, and >70% at the disease progression visit). At all assessments, the mean EORTC-QLQ-30 global health status score was significantly better ($p<0.05$) and clinically meaningful for patients receiving trametinib+dabrafenib compared with those receiving vemurafenib.[49] Similarly, at almost every assessment, the EORTC-QLQ-30 functional health scores were found to be statistically significantly better (and clinically meaningful) for patients receiving trametinib+dabrafenib compared with those receiving vemurafenib. The EORTC-QLC-C30 symptom domain scores also tended to be better for the cohort treated with trametinib+dabrafenib compared with those treated with vemurafenib. The exceptions were the scores for constipation (all assessments) and dyspnoea (weeks 16 and 32) which were higher for patients receiving vemurafenib than they were for the cohort treated with trametinib+dabrafenib. The ERG, however, notes that the confidence intervals for all EORTC-QLQ-30 scores were wide.

EQ VAS scores were similar at baseline for both treatment groups (68.3 for patients treated with trametinib+dabrafenib and 68.8 for vemurafenib monotherapy patients). At all assessments, the mean VAS scores for patients receiving trametinib+dabrafenib improved relative to the baseline score, whilst the mean scores for patients receiving the monotherapy decreased. For all assessments, the differences between scores for the two treatment arms were found to be statistically significantly better ($p<0.05$), and clinically meaningful, for patients treated with trametinib+dabrafenib compared with those for patients treated with vemurafenib monotherapy.

Utility scores, calculated from data collected using the EQ-5D questionnaire, were shown to be comparable between the treatment arms at baseline (0.751 for patients treated with trametinib+dabrafenib and 0.715 for patients treated with vemurafenib monotherapy).[43] For all assessments, the differences between scores for the two treatment arms were found to be statistically significantly better ($p<0.05$), and clinically meaningful, for patients treated with trametinib+dabrafenib compared with those for patients treated with vemurafenib monotherapy.[49]

Mean baseline FACT-M Subscale scores were similar in both treatment arms (53.1 for patients treated with trametinib+dabrafenib and 51.7 for patients treated with vemurafenib). At all assessments, the mean FACT-M Subscale scores for patients receiving trametinib+dabrafenib improved relative to the baseline score, whilst the mean scores for patients receiving the monotherapy decreased. For all assessments, the differences between scores for the two treatment arms were found to be statistically significantly better ($p<0.001$), and clinically meaningful, for patients treated with trametinib+dabrafenib compared with those for patients treated with vemurafenib monotherapy.[49]

The results from the analyses of HRQoL data collected during the COMBI-v trial suggest that, compared with treatment with vemurafenib, treatment with trametinib+dabrafenib results in statistically significant and clinically meaningful improvements in many aspects of HRQoL. The ERG, however, cautions that the lack of study blinding may have had an influence on the HRQoL scores reported by patients in the COMBI-v trial.

4.8 Subgroup analyses

The company conducted a series of subgroup analyses within the COMBI-d and COMBI-v trials (CS, Figure 19, Figure 20, Figure 21 and Figure 22). The ERG agrees with the company that the results of all the subgroup analyses are consistent with the results of the ITT analyses (in favour of trametinib+dabrafenib). No statistically significant p-values for interaction were observed. The company provided the results of the tests for subgroup differences during the clarification process.

The subgroup analyses 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).

The ERG notes that the final NICE scope specifies that if evidence allows, consideration should be given to trametinib+dabrafenib as a first-line therapy or after treatment with immunotherapy. The company states (CS, p9) that the clinical evidence presented in the CS relates almost entirely to the use of trametinib+dabrafenib as a first-line therapy. The ERG agrees that there is no clinical evidence available in the CS that allows consideration of trametinib+dabrafenib as a second-line treatment following treatment with immunotherapy.

4.8.1 Adverse events

The company presents comprehensive analyses of safety events from the COMBI-d and COMBI-v trials (CS, p136 to p153). To offer the most complete representation of AEs, the data analysed were taken from the most recent data cut for each trial. The ERG notes that the date of the most recent data cut differs depending on the type of AE being reported.

4.8.2 Duration of treatment exposure

Tables 49 and 50 of the CS show that patients in all arms of the COMBI-d (January 2015 data cut) and COMBI-v trials (data cut March 2015) were treated with the planned therapeutic doses of the study drugs. In both trials, the median duration of treatment with trametinib+dabrafenib was 11 months. The median duration of treatment with dabrafenib+placebo and vemurafenib monotherapy was 8 months and 6 months respectively.

4.8.3 Overview of adverse events

Table 51 of the CS provides an overview of the AEs from the COMBI-d and COMBI-v trials. The company reports (CS, p137):

- almost all patients in the COMBI-d and COMBI-v trials experienced an AE (97% in both arms of the COMBI-d trial and 99% in both arms of the COMBI-v trial)
- in the COMBI-d trial, AEs leading to treatment discontinuation, dose interruption or dose reduction were more frequent in the trametinib+dabrafenib arm than in the dabrafenib+placebo arm (32% versus 19%)
- In the COMBI-v trial, the frequency of AEs leading to treatment discontinuation, dose interruption or dose reduction was similar in both arms of the trial (32% versus 32%)
- there was a similar frequency of serious AEs (SAE) across the trials, ranging from 37% to 43%
- of the 14 fatal SAEs, one was considered to be treatment related and occurred in the dabrafenib+placebo arm of the COMBI-d trial.

4.8.4 Most commonly reported adverse events

Table 52 of the CS provides a breakdown of the AEs from the COMBI-d (January 2015 data cut) and COMBI-v trials (March 2015 data cut) that were reported at a frequency ≥15%. The ERG notes that for patients treated with trametinib+dabrafenib and dabrafenib+placebo, approximately 50% of AEs were of grades 1 or 2. For patients treated with vemurafenib, 44% of AEs were of grades 1 or 2.

The most frequently occurring AEs associated with trametinib+dabrafenib were pyrexia (56%), fatigue (35%), nausea (35%), headache (33%), chills (32%), diarrhoea (32%), rash (25%), vomiting (28%) hypertension (27%), arthralgia (25%), and cough (22%).

For patients treated with dabrafenib+placebo, the most frequently occurring AEs were fatigue (37%), pyrexia (33%), arthralgia (31%), headache (30%), nausea (27%) and rash (22%).

For patients treated with vemurafenib, the most frequently occurring AEs were arthralgia (52%), rash (43%), diarrhoea (39%), nausea (37%), fatigue (34%), headache (24%), hypertension (23%), pruritus (22%), pyrexia (21%), and decreased appetite (20%).

The ERG agrees with the company that patients treated with trametinib+dabrafenib experienced substantially fewer dermatological AEs compared with patients treated with a BRAF inhibitor (hyperkeratosis=6% versus 30%, hand-foot syndrome=5% versus 22%, alopecia=8% versus 34%, skin papilloma=2% versus 22%).

The company also highlights that patients in the trametinib+dabrafenib arm experienced fewer photosensitivity reactions and sunburn than patients treated with vemurafenib (3% versus 23% and <1% versus 15%)

4.8.5 Grade 3 and 4 adverse events

Grade 3 and grade 4 AEs reported by ≥3% of patients in the COMBI-d and COMBI-v trials are listed in Table 12. The ERG notes that the highest rates of grade 3 and grade 4 AEs were experienced by patients in the vemurafenib arm of the COMBI-v trial (66% compared with 51% in the trametinib+dabrafenib arm and 50% in the dabrafenib+placebo arm).

The most commonly reported grade 3 or grade 4 AEs associated with trametinib+dabrafenib were hypertension (10%), pyrexia (6%) and neutropenia (4%).

The most commonly reported grade 3 or grade 4 AEs associated with dabrafenib+placebo were hypertension (6%), basal cell carcinoma (6%) squamous cell carcinoma of the skin (5%), squamous cell carcinoma (4%) and anaemia (4%).

The most commonly reported grade 3 or grade 4 AEs associated with vemurafenib were keratoacanthoma (10%), squamous cell carcinoma of the skin (9%), rash (9%), hypertension (9%), squamous cell carcinoma (6%).

Table 12 Grade 3 and grade 4 adverse events (≥3% patients) in the COMBI-d and COMBI-v trials

	COMBI-d (January 2015)				**COMBI-v (March 2015)**			
	Trametinib+dabrafenib (N=209)		Dabrafenib+placebo (N=211)		Trametinib+dabrafenib (N=350)		Vemurafenib (N=349)	
Median follow-up (months)	20		16		19		15	
Grade	**Any**	**G3 or G4**	**Any**	**G3 or G4**	**Any**	**G3 or G4**	**Any**	**G3 or 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)

ALT= alanine aminotransferase; AST= aspartate aminotransferase; GGT= gamma glutamyl transferase; SCC=squamous cell carcinoma: G3=grade 3; G4=grade 4
Source: CS, adapted from Table 53

4.8.6 Serious adverse events

The rates of serious SAEs experienced by ≥1% of patients are reported (CS, Table 55). The most common SAEs associated with treatment with trametinib+dabrafenib were pyrexia (16%), decreased ejection fraction (6%) and chills (4%). The most common SAEs associated with dabrafenib+placebo were cutaneous squamous cell carcinoma and squamous cell carcinoma (9%), pyrexia (7%), and basal cell carcinoma (6%). The most common SAE associated with vemurafenib was cutaneous squamous cell carcinoma and squamous cell carcinoma (15%).

4.8.7 Adverse events leading to treatment discontinuation, dose interruption or dose reductions

The company reports (CS, p150) that:

- in the COMBI-d trial 11% of patients in the trametinib+dabrafenib arm and 7% of patients in the dabrafenib+placebo arm discontinued study treatment due to AEs (January 2015 data cut)
- in the COMBI-v trial, 16% of patients in the trametinib+dabrafenib arm and 14% of patients in the vemurafenib arm discontinued study treatment due to AEs (March 2015 data cut)
- in the COMBI-d trial dose interruptions were required for 56% of patients in the trametinib+dabrafenib arm and 37% of patients in the dabrafenib+placebo arm (January 2015 data cut)
- in the COMBI-v trial, 55% of patients in the trametinib+dabrafenib arm and 56% of patients in the vemurafenib arm had a treatment dose interruption (April 2014 data cut)
- pyrexia (≤4%) and decreased ejection fraction (≤3%) were the most common reasons for patients in the trametinib+dabrafenib arms discontinuing treatment
- pyrexia (≤33%) was the most common reason for patients to discontinue treatment in the trametinib+dabrafenib arms and the dabrafenib+placebo arm. Rash (14%) was the most common reason for dose interruption for patients treated with vemurafenib (CS, Table 59).

The company reports (CS, p152) the results of subgroup analyses of AEs in the COMBI-d and COMBI-v trials by age group: <65 years and ≥65 years. The percentage of patients reporting any AE was similar across age groups and treatment arms; however, the percentage of patients with grade 3 or grade 4 AEs, SAEs and AEs leading to discontinuation or dose reduction was higher (in both treatment arms) for the patients aged ≥65 years compared with the younger patient group.

4.8.8 Adverse events of special interest

The company presents (CS, p142) an analysis of AEs of special interest (AESI). The AESIs are described by the company as either a known class AE, AEs that were identified pre-

clinically or in clinical trials or AEs that are a possible threat to life. The company states (CS, p142) that the AESIs recorded in the COMBI-d and COMBI-v trials for dabrafenib, trametinib and vemurafenib were in accordance with the AEs known to be associated with each particular treatment. Full details and a discussion of selected individual AESIs (pyrexia, cutaneous squamous cell carcinoma, new primary melanoma, skin-related toxicities, hypertension, bleeding events, cardiac-related events, ocular events, hepatic disorders, renal insufficiency, oedema events, QT prolongation, neutropenia, pancreatitis, pulmonary embolism and deep vein thrombosis) are presented in the CS (p142). The results of clinical chemistry and haematology assessments are also described in the CS (p153).

4.8.9 Summary of adverse events

Almost all of the patients in the COMBI-d and COMBI-v trials experienced an AE, approximately half of which were of grade 1 or grade 2 severity. The company reports that that the AEs recorded in the COMBI-d and COMBI-v trials were consistent with the known AE profiles of the individual treatments. The AEs associated with trametinib+dabrafenib (most frequently occurring, grade 3 and 4 and SAE) were pyrexia, hypertension, headache, nausea, vomiting and diarrhoea. The company asserts (CS, p175) that all of these AEs are clinically manageable. Treatment with vemurafenib and dabrafenib+placebo appear to be associated with increased incidences of carcinoma and the highest rates were reported by patients treated with vemurafenib. The ERG agrees with the company's statement (CS, p175) that the incidences of skin-related AEs (hyperkeratosis, hand/foot syndrome, alopecia, squamous cell carcinomas and new primary melanomas) occur less frequently in patients treated with trametinib+dabrafenib compared with patients treated with a BRAF inhibitor. In addition, greater numbers of patients treated with vemurafenib reported experiencing photosensitivity, arthralgia and rash compared with patients treated with trametinib+dabrafenib.

4.9 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.9.1 Comparison of trametinib+dabrafenib with BRAF monotherapies

The company did not conduct any indirect or multiple treatment comparisons in its evaluation of trametinib+dabrafenib with either dabrafenib or vemurafenib. The ERG agrees that the company has presented RCT data for the comparisons listed in the scope. However, the ERG is of the opinion that the evidence in the CS would be more complete if data from the key RCTs conducted in patients with unresectable or metastatic melanoma were considered (Table 13).

In this section, the ERG provides an overview of the available evidence for the efficacy of dabrafenib and vemurafenib monotherapies. The ERG also explores the possibility of constructing an evidence network to inform a comparison of trametinib+dabrafenib with pembrolizumab and ipilimumab. The ERG accepts that the final NICE scope did not require the company to address the latter comparisons.

4.9.2 Dabrafenib monotherapy

Evidence for the effectiveness of dabrafenib monotherapy is available from the Phase III BREAK-3[50-52] trial. In this trial dabrafenib was compared with dacarbazine. A comparison of the characteristics of patients recruited to BREAK-3 and the COMBI-d trial shows that, compared with the BREAK-3 trial, the COMBI-d trial included a greater proportion of female patients (47% vs 40%). However, for other baseline characteristics (age, disease stage, ECOG status, tumour, node, metastases staging, LDH levels and number of organs with metastases involved) the two trials were broadly similar.

Results show that the median PFS for patients in the dabrafenib arm of the BREAK-3 trial was lower than that for patients in the dabrafenib arm of the COMBI-d trial (6.9 months versus 8.8 months). However, the median OS for patients in the dabrafenib arm of the BREAK-3 trial was higher than that reported for patients in the dabrafenib arm of the COMBI-d trial (20.1 months versus 15.6 months).

4.9.3 Vemurafenib monotherapy

Evidence for the effectiveness of vemurafenib monotherapy is available from the BRIM-3[53-55] trial and also from the CoBRIM[46,56] trial. The BRIM-3 trial was designed to compare the effectiveness of vemurafenib with dacarbazine, whilst the CoBRIM trial was designed to compare cobimetinib in combination with vemurafenib with vemurafenib. The baseline characteristics of patients recruited to the COMBI-v, BRIM-3 and CoBRIM trials were broadly similar.

Median PFS results for patients in the vemurafenib arms of all three trials are similar: 7.3 months, 6.9 months and 7.2 months for patients in the COMBI-v, BRIM-3 and CoBRIM trials respectively. These figures are similar to the results for patients in the dabrafenib arm of the BREAK-3 trial (6.9 months) but lower than the result for the patients in the dabrafenib arm of the COMBI-d trial (8.8 months).

Median OS results for patients treated with vemurafenib are also similar for patients recruited to the COMBI-v and CoBRIM trials (18.0 months and 17.4 months respectively) but are noticeably lower for patients recruited to the earlier BRIM-3 trial (13.6 months), possibly

due to the limited number of post-study treatments available to patients at the time of the BRIM-3 trial.

4.9.4 Indirect treatment comparison (dabrafenib vs vemurafenib)

As both the BRIM-3 and BREAK-3 trials include dacarbazine as a comparator it is possible to undertake an indirect treatment comparison (ITC) for OS and PFS, and ITCs were presented in the CS for NICE TA321[12] comparing dabrafenib vs vemurafenib. The results from these ITCs show a trend in favour of dabrafenib over vemurafenib for both PFS and OS, but the treatment difference was not found to be statistically significant for either outcome. However, during TA321[12] the ERG questioned the validity of the approach used to conduct the ITCs as key underlying assumptions were not met. First, constant hazard ratios for both PFS and OS data within both the BREAK-3 and BRIM-3 trials were not evident. Second, a comparison of dacarbazine OS data from the two trials indicated that constant proportional hazards were not supported ($p<0.001$). The ERG therefore concluded that there was insufficient evidence to support the results of the comparison between dabrafenib and vemurafenib. However, it should be noted that during TA321[12] the AC concluded that it was likely that dabrafenib and vemurafenib did not differ in clinical effectiveness and that it would not be unreasonable to assume that they have similar effect.

4.10 Ipilimumab and pembrolizumab

Ipilimumab and pembrolizumab are both immunotherapies that have received NICE recommendations[10,13-15] for use in patients with unresectable (advanced or metastatic) malignant melanoma.

NICE TA366[15] focused on the treatment of patients with unresectable (advanced or metastatic) malignant melanoma who had not been previously treated with ipilimumab. The main evidence presented in the CS for that appraisal came from the KEYNOTE 006[19] trial. The KEYNOTE 006 trial is a Phase III trial which included the comparison of pembrolizumab with ipilimumab. The median PFS (based on investigator assessment) for patients receiving pembrolizumab (10mg/kg every 3 weeks) is 7.2 months, whilst that for patients receiving ipilimumab is 3.3 months. Only median PFS results are available from this trial as it was stopped early for benefit.

Comparing median PFS results for patients treated with immunotherapy with those for patients treated with BRAF inhibitors is not straightforward. First, the use of immunotherapies is not restricted to patients with BRAF V600 mutation-positive melanoma and there are no published results for that subgroup. Second, whilst the majority of patients treated with a BRAF inhibitor achieve a rapid response, that response is often short-lived

(approximately 6 months).[17] In contrast, the proportion of patients who benefit from ipilimumab is limited (10%)[18] but for those that do benefit, treatment can be durable (2 to 3 years). The ERG notes that treatment with pembrolizumab is associated with fewer side effects than ipilimumab and appears to benefit more patients (30% to 40%);[57] however, long-term outcomes for patients treated with pembrolizumab are at present unclear.

The ERG also notes that nivolumab[26] (another immunotherapy) is currently being appraised for treating advanced, unresectable or metastatic melanoma and that the NICE FAD for this appraisal is expected to be published in February 2016.

4.10.1 Indirect treatment comparison (immunotherapy vs BRAF inhibitor)

In theory, a network could be constructed to link ipilimumab and pembrolizumab with trametinib+dabrafenib (Figure 2).

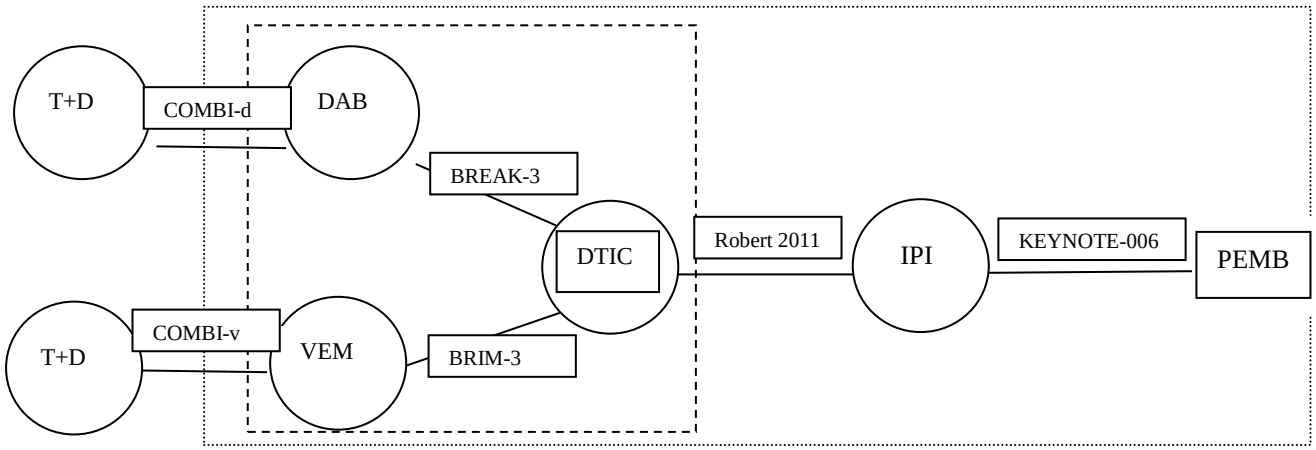

Figure 2 Network of evidence for first-line treatment

DAB=dabrafenib; DTIC=dacarbazine; IPI=ipilimumab; PEMB=pembrolizumab; T+D=trametinib+dabrafenib; VEM=vemurafenib

However, the ERG considers that such an ITC would not yield meaningful results. Analyses carried out by the ERG during previous NICE appraisals of dabrafenib (TA321)[12] and pembrolizumab (TA366[15]) have shown that sub-sections of these networks are flawed. Issues relating to the dabrafenib – dacarbazine – vemurafenib network (within dashed square box) have been summarised in Section 4.9.4. Essentially, the ITC methodology employed was based on the assumptions that treatment effects were proportional both between comparator arms within trials and across trials. This assumption was violated for

most comparisons. In the ITC carried out as part of NICE TA366[15] (dotted rectangular box) the company used an ITC methodology that did not rely on the assumption of proportional hazards. However, results from using this method did not reflect trial hazard ratios for the comparison of ipilimumab versus pembrolizumab and doubt was cast on the reliability of the method. In addition, the ERG had concerns that the results from the pembrolizumab and ipilimumab trials were for the whole population and might not be reflective of the experience of patients with a BRAF V600 mutation.

In summary, the ERG considers that it was not possible to carry out an ITC using data from Phase III trials that included trametinib+dabrafenib, dabrafenib, vemurafenib, pembrolizumab and ipilimumab due to the methodological challenges associated with using the published data.

Table 13 Key characteristics and results of RCTs conducted in a BRAF V600 patient population

Trial & design	Patient N	BRAF inhibitor monotherapy	Other treatment	Patient population	Median PFS, months (95% CI)		Median OS, months (95% CI)	
					BRAF mono	Other	BRAF mono	Other
RCTs of BRAF inhibitors								
COMBI-d Double-blind	423	Dabrafenib+ placebo	Trametinib+ dabrafenib	Previously untreated, unresectable or metastatic BRAF V600 mutation-positive melanoma	8.8 (5.9 to 9.3)	11.0 (8.0 to 13.9)	18.7 (15.2 to 23.7)	25.1 (19.2 to NR)
BREAK-3[51,52,58] Open-label	250	Dabrafenib	Dacarbazine	Previously untreated, unresectable or metastatic BRAF V600 mutation-positive melanoma	*6.9 (5.2 to 9.0)	*2.7 (1.5 to 3.2)	20.1 (16.8 to 24.4)	15.6 (12.7 to 21.2)
COMBI-v Open-label	704	Vemurafenib	Trametinib+ dabrafenib	Previously untreated, unresectable or metastatic BRAF V600 mutation-positive melanoma	*7.3 (5.8 to 7.8)	*12.6 (10.7 to 15.5)	18.0 (15.6 to 20.7)	25.6 (22.6 to NR)
CoBRIM[46,56,59] Double-blind	495	Vemurafenib	Vemurafenib+ cobimetinib	Previously untreated, unresectable or metastatic BRAF V600 mutation-positive melanoma	7.2 (5.6 to 7.5)	12.3 (9.5 to 3.4)	17.4 (15 to 19.8)	22.3 (20.3 to NR)
BRIM-3[53,55,60] Open-label	675	Vemurafenib	Dacarbazine	Previously untreated, unresectable or metastatic BRAF V600E mutation-positive melanoma	6.9 (6.1 to 7)	1.6 (1.6 to 2.1)	13.6 (12.0 to 15.41)	9.7 (7.9 to 12.8)
RCT comparing immunotherapies								
		Intervention	**Comparator**		**Intervention**	**Comparator**	**Intervention**	**Comparator**
KEYNOTE-006[19] Open-label	834 107 (38.5%) with BRAF mutation	Pembrolizumab	Ipilimumab	Previously untreated unresectable or metastatic melanoma and known BRAF mutation status. 33% of patients had received prior treatment (including a BRAF inhibitor)	4.1 (2.9 to 6.9) Overall population	2.8 (2.8 to 2.9) Overall population	Not reached	Not reached

* based on investigator-assessment. CI=confidence interval; PFS=progression-free survival; mono=monotherapy; OS=overall survival
Source: CS, adapted from Table 11 and published papers

4.11 Pooling clinical data from the COMBI-d and COMBI-v trials

The ERG notes that, in the CS, the company has presented efficacy results from the COMBI-d and COMBI-v trials separately. However, the company's cost effectiveness analyses uses survival data that have been pooled from both of these trials.

The arguments presented by the company for pooling data from the two trials are, essentially, that:

1. Trial designs and patient populations are nearly identical
2. There is clinical consensus that dabrafenib and vemurafenib are equivalent in terms of efficacy
3. Pooling the data increases the precision of the AUC analyses.

Similarity between COMBI-d and COMBI-v trial designs and patient populations

Details provided in Table 14 of the CS show that, in terms of population, inclusion criteria, main exclusion criteria, intervention, concomitant medication, and compliance the COMBI-d and COMBI-v trials are identical. Furthermore, identical methods were used to assign patients to the different arms of the COMBI-d and COMBI-v trials. The stratification factors that were used were also identical (LDH [>ULN versus ≤ULN] and BRAF mutation [V600E versus V600K]). The two tables in the CS showing the baseline demographic and disease characteristics of the patients recruited to the COMBI-d and COMBI-v trials (Table 23 and Table 24 respectively) show that the characteristics of the patients in both arms of both trials are very similar. The similarity of patient characteristics supports the company's argument for pooling data from the COMBI-d and COMBI-v trials.

However, the COMBI-d trial was blinded and placebo controlled, whilst the COMBI-v trial was neither blinded nor placebo controlled. The key issue is the extent to which both the lack of blinding and the lack of a placebo may have affected the results from the COMBI-v trial.

Clinical equivalence

There are no data from head-to-head trials to show whether or not dabrafenib and vemurafenib are equally efficacious. However, during the NICE appraisal of dabrafenib monotherapy (TA321[12]) the AC "…concluded that it was likely that dabrafenib and vemurafenib did not differ in clinical effectiveness and that it would not be unreasonable to assume that they have similar effect". Furthermore, calculations carried out by the ERG using IPD data show that there is no statistical

difference in terms of OS between dabrafenib and vemurafenib in the COMBI-d and COMBI-v trials (Log-rank statistics: 1.125, p=0.290). There is, therefore, statistical evidence to support pooling data from the two trials.

Precision of the AUC analyses

In terms of trametinib+dabrafenib therapy, the K-M OS curves are almost identical in both the COMBI-d and COMBI-v trials (Log-rank statistic: -0.0004, p=0.984). This means that there is likely to be very little difference in the results derived from an assessment of AUC irrespective of whether the data are pooled or whether data are used from either the COMBI-d trial or the COMBI-v trial. The ERG, therefore, completely rejects the argument that pooling the data increases the accuracy of the company's AUC analysis.

Additional points to consider regarding pooling of data from the COMBI-d and COMBI-v trials

The ERG has a number of concerns relating to whether pooled OS IPD from the COMBI-d and COMBI-v trials should have been used in the company's economic model.

First, the ERG recognises the similarity in trial design, patient characteristics and statistical evidence that the IPD data from the trametinib+dabrafenib arms and the monotherapy arms of the COMBI-d and COMBI-v trials are not statistically significantly different. However, there are no statistical tests that can show the extent to which trial results are subject to bias.

Second, the COMBI-d trial was a blinded and placebo controlled trial, whilst the COMBI-v trial was an open-label trial that did not involve a placebo. The methodology employed in the COMBI-d trial is, therefore, considered to be "gold standard", whilst the method used in the COMBI-v trial is recognised as having limitations and potential bias. The ERG considers that pooling data from a high quality blinded trial (COMBI-d) with data from a trial with outcomes that are subject to bias (COMBI-v) may actually reduce the reliability of the available trial results.

Third, statistical tests show that, in terms of OS, the IPD from the trametinib+dabrafenib arms of the COMBI-d and COMBI-v trials are not significantly different, and also that IPD from the two monotherapy arms, although more dissimilar than those for combination therapy, are also not statistically significantly different. However, examination of the individual OS K-M analyses of the two trials shows that the survival profiles over time for the two trials do appear to be different. The K-M OS

data from the COMBI-d trial (CS, Figure 12, p106) suggest that after about 6 months the mortality risk for patients in both arms of the trial may be equal. This similarity in mortality risk may be as a result of the placebo controlled and blinded nature of the trial. In contrast, examination of the K-M OS data from the COMBI-v trial (CS, Figure 14, p113) suggests equal mortality risk until about month 3, the curves then split but run parallel from about month 4 until about month 10 when they diverge until month 24, at which point only a small number of patients are included in the analysis and thus results may be unreliable.

The ERG considers that a comparison of the separate OS K-M data from the COMBI-d and COMBI-v trials suggests that survival profiles over time are different, and that this supports an argument for not pooling the data from the two trials.

Fourth, during the clarification process the ERG requested treatment data for patients who continued to receive study treatment post investigator-assessed progression (specifically more than 15 days post progression, at which point continuation of treatment was considered to be deliberate). These data show that, although around 30% of patients in both arms of both trials remained on treatment post progression, there was considerable variation in the length of time patients remained on treatment, ranging from 205.4 days in the trametinib+dabrafenib arm of the COMBI-d trial to only 71.1 days in the vemurafenib arm of the COMBI-v trial.

The ERG considers that these differences are likely, in part, to be driven by the lack of a blinding and the lack of a placebo in the COMBI-v trial and may have had an impact on the duration of patient OS. Furthermore, the differences in duration of study treatment post progression indicate that although the baseline characteristics may have been similar, the experiences of patients during the period they were enrolled in the two trials are different.

In conclusion, the ERG considers that results from a high quality blinded and placebo controlled trial (COMBI-d) are more likely to show the true effectiveness of a drug than results from an unblinded, non-placebo controlled trial (COMBI-v), or results generated from pooling data from a blinded and placebo controlled trial with those from an unblinded, non-placebo controlled trial. The rationale behind the company's use of pooled OS data in their model may be based on pragmatism. Analyses undertaken by the ERG show that use of pooled OS data in the company model generates cost effectiveness results that make trametinib+dabrafenib appear much

more cost effective (compared to either dabrafenib or vemurafenib monotherapy) than those generated using OS data only from the COMBI-d trial.

4.12 Summary and conclusions of the clinical effectiveness section

4.13 Clinical summary

Direct RCT evidence is available for the comparison of trametinib+dabrafenib with dabrafenib+placebo and for the comparison of trametinib+dabrafenib with vemurafenib. Results from the COMBI-d trial demonstrate that compared to treatment with dabrafenib, trametinib+dabrafenib statistically significantly improves OS, PFS and ORR. Results from the COMBI-v trial demonstrate that compared to treatment with vemurafenib, trametinib+dabrafenib statistically significantly improves OS, PFS and ORR. The ERG agrees with the company that trametinib+dabrafenib appears to be clinically effective when compared with dabrafenib+placebo and when compared with vemurafenib. Results from the COMBI-d trial show that the incidence of grade 3 or 4 AEs was slightly lower for patients receiving trametinib+dabrafenib than for patients receiving dabrafenib+placebo (45% versus 50%). Similarly, results from the COMBI-v trial show that the incidence of grade 3 or 4 AES was slightly lower for patients receiving the combination treatment than it was for patients receiving vemurafenib monotherapy (57% versus 66%). In addition, patients treated with trametinib+dabrafenib experienced substantially fewer new skin cancers compared with patients treated with a BRAF inhibitor.

4.14 Key issues and uncertainties

All of the patients in the COMBI-d and COMBI-v trials were relatively well as demonstrated by their ECOG PS of 0 to 1. All of the patients in COMBI-d and COMBI-v trials were given a BRAF inhibitor as a first-line treatment. In current NHS practice, some patients with BRAF mutation-positive melanoma can receive ipilimumab or pembrolizumab as a first-line treatment for their mutation-positive melanoma instead of a BRAF inhibitor. The ERG notes that treatment sequencing for this group of patients is uncertain.

The only comparators specified in the NICE scope were dabrafenib and vemurafenib monotherapies. The ERG notes that, in clinical practice, ipilimumab and pembrolizumab (the latter since November 2015) are also treatment options recommended by NICE for patients with unresectable or advanced BRAF V600 mutation-positive melanoma. The ERG notes that the wording of the final scope

issued by NICE states that patients who are relatively well with slowly progressing disease are likely to receive immunotherapy.

The licensed indication, the NICE scope and the company's decision problem all describe trametinib+dabrafenib as a treatment for patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma; there is no mention of line of treatment. The clinical evidence presented in the CS is derived from two key trials that recruited only patients with untreated disease. Therefore, there is no clinical evidence in the CS to support the use of trametinib+dabrafenib in patients who have received prior treatment for their advanced disease.

Due to the limitations imposed on patient recruitment, there is no clinical evidence from the COMBI-d or the COMBI-v trials to support the use of trametinib+dabrafenib in patients with a PS of 2 or higher, or for patients with brain metastases. Clinical advice to the ERG is that patients with an ECOG score of 2 or higher and patients with brain metastases are treated in UK clinical practice.

The COMBI-v trial was an open-label, unblinded RCT that did not included a BIRC assessment of radiological outcomes. It is unclear to what extent the key outcomes of the trial may be biased (PFS, ORR and HRQoL).

The company used pooled data from the COMBI-d and the COMBI-v trials in the cost effectiveness analysis. The ERG considers that results from a high quality blinded and placebo controlled trial (COMBI-d) are more likely to show the true effectiveness of a drug than results from an unblinded, non-placebo controlled trial (COMBI-v), or results generated from pooling data from a blinded and placebo controlled trial with those from an unblinded, non-placebo controlled trial.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by Novartis Pharmaceuticals UK Limited in support of the use of trametinib in combination with dabrafenib (compared with BRAF inhibitor monotherapy) for the treatment of advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company also provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.2 The company's review of cost effectiveness evidence

5.2.1 Objective of cost effectiveness review

The company undertook searches to identify economic studies, including cost effectiveness analyses, relevant to the decision problem. Details of the search strategies employed by the company are included in Appendix 8.11 of the CS. Four databases were searched, namely Medline (via Embase.com platform), Medline In-process (via PubMed platform), EMBASE (via Embase.com platform) and Cochrane database for economic review. All the searches were carried out on 13 July 2015.

In addition, the abstracts from the following conferences (held between 2012 and October 2015) were hand searched:

- 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 Organisation (ECO)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

The websites of the following organisations were also searched:

- European Medicines Agency (EMA)
- Food and Drug Administration (FDA)
- National Institute for Health and care Excellence (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)

- Agency for Healthcare Research and Quality (AHRQ).

In addition, the clinicaltrials.gov website was searched to identify trials in progress that were investigating the interventions of interest.

5.2.2 Eligibility criteria used in the study selection

The inclusion criteria used to select studies are presented in Table 14.

Table 14 Economic evaluation search inclusion/exclusion criteria

Parameter	Inclusion criteria
Population	Adults aged ≥ 18 years with BRAF V600 mutation positive metastatic melanoma. First or second-line therapy for the metastatic stage
Interventions	There were no restrictions on interventions or comparators
Study design	Evidence was not limited on the basis of study design
Countries	Any country
Language restrictions	English only
Publication timeframe	Database inception to 13 July 2015 for literature searches and 2012 to October 2015 for conference abstracts

QALYs=quality adjusted life years
Source: CS, Table 73

5.2.3 Included and excluded studies

The company has provided details of the results of the search, including the PRISMA diagram, in the CS (Appendix 8.11). Only one relevant study[61] was identified. This abstract describes a study that estimated the cost effectiveness of trametinib+dabrafenib compared with vemurafenib and dacarbazine for patients with BRAF V600 mutation-positive malignant melanoma.

5.2.1 Findings from cost effectiveness review

The company concluded that the relevance of the findings from the one identified study[61] were limited as:

- current prices are different from those assumed in the publication
- updated efficacy data are now available
- the efficacy of trametinib in combination with dabrafenib versus dabrafenib was not reported.

5.2.2 Conclusions of the cost effectiveness review

The search strategy only identified one potentially relevant study.[61] However, on examining this study, the company concluded that it was of limited relevance to the current decision problem.

5.2.3 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and stated inclusion criteria and is confident that the company did not miss any relevant published papers. However, searches carried out by the ERG to identify relevant papers published after July 2015 (the date on which the company's searches were carried out) have identified one further study[62] of interest. This study[62] assessed the cost effectiveness of trametinib+dabrafenib, compared with vemurafenib, as a first-line therapy for patients with BRAF V600 mutation-positive melanoma in the Swiss setting. The study concluded that, at a willingness to pay threshold of CHF100,000 and US prices, trametinib+dabrafenib is unlikely to be cost effective compared with vemurafenib monotherapy.

The ERG notes that the company also carried out a literature search to identify studies reporting HRQoL. Full details of the search strategy used by the company are not provided in the CS, neither are the eligibility criteria employed by the company. However, a PRISMA flow diagram and a list of studies that met the company's eligibility criteria are provided in Appendix 8.11. Although this list of studies is interesting, the company does not provide their rationale for concluding that the only studies providing relevant HRQoL data are the COMBI-d and COMBI-v trials.

5.3 Overview of company's economic modelling

5.3.1 Description of company's economic model

A schematic of the economic model submitted by the company is provided in the CS and is reproduced in Figure 3. The company's model compares trametinib+dabrafenib with BRAF inhibitor monotherapy (i.e. either dabrafenib monotherapy or vemurafenib monotherapy). It is a partitioned survival model that comprises three mutually exclusive health states: progression-free (i.e. PFS), post-progression (i.e. PPS) and death. All patients enter the model in the progression-free state. At the beginning of each time period patients can either remain in the same health state or progress to a worse health state, i.e. patients in the progression-free state can either move to the post-progression state or the death health state; whilst patients in the post-progression state can only move to the death health state. The area under the curve (AUC) method is used to determine the proportion of patients in each of the three health states during each model cycle. The proportion of patients in the PPS state is estimated as the difference between OS and PFS.

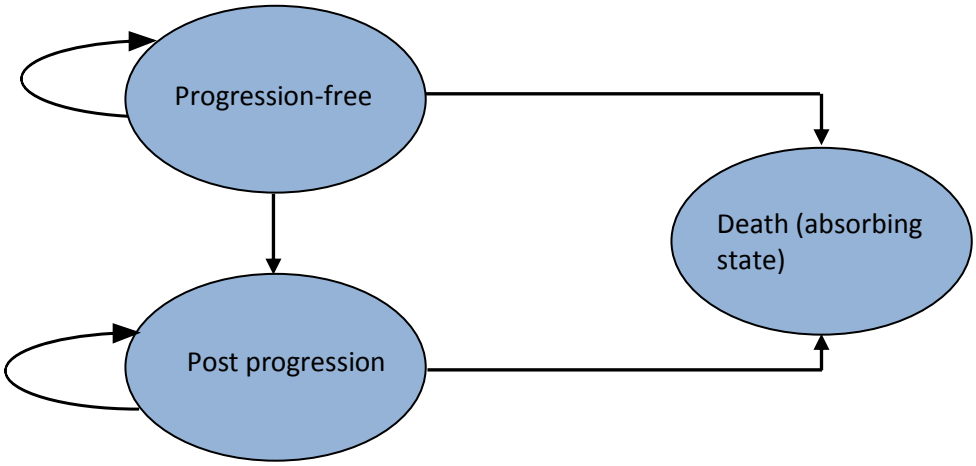

Figure 3 Schematic of company's model
Source: CS, Figure 28

Data from two Phase III trials, COMBI-d and COMBI-v, are used in the economic model. Dabrafenib and vemurafenib are considered to have equivalent efficacy and time to event data from the intervention and comparator arms of the COMBI-d and COMBI-v trials have been pooled. However, within the company model, dabrafenib and vemurafenib are differentiated by their effects on safety and quality of life, which have been modelled in line with results from the COMBI-d and COMBI-v trials. The company reports that the impact of any heterogeneity between studies is accounted for in their probabilistic sensitivity analysis (PSA).

The model has been developed in MS Excel and employs a cycle length of 1 week (no half-cycle correction). The time horizon is 30 years and health effects are measured in quality adjusted life years (QALYs). The perspective is that of the NHS and future cost and outcomes are discounted at an annual rate of 3.5%.

Variants of the company's model structure have been used in the modelling of metastatic oncology for numerous STAs, including five recent NICE STAs which considered treatments for patients with advanced melanoma (TA268,[10] TA269,[11] TA321,[12] TA357[14] and TA366[15]).

5.3.2 Population

The company's economic evaluation includes patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. This is consistent with the patient group defined in the final NICE scope and in the European marketing authorisation[32] for the combination of trametinib with dabrafenib.

5.3.3 Intervention and comparator technology

The intervention (trametinib+dabrafenib) and comparator (a BRAF inhibitor) are implemented in the model in line with their respective marketing authorisations[35,36,63] (Table 15).

Table 15 Drug doses and dosing schedules

Drug	Type of administration	Daily dose (mg)	Basis of daily dose	Source
Dabrafenib (combination)	Oral	300	Per patient	Dabrafenib SPC[35]
Trametinib (combination)	Oral	2	Per patient	Trametinib SPC[36]
Dabrafenib	Oral	300	Per patient	Dabrafenib SPC[35]
Vemurafenib	Oral	1920	Per patient	BNF[63]

Source: CS, Table 82

5.3.4 Perspective, time horizon and discounting

The economic evaluation was undertaken from the perspective of the NHS. The time horizon was set at 30 years and, in line with the NICE Methods Guide to Technology Appraisal,[64] both costs and outcomes were discounted at 3.5%.

5.3.5 Treatment effectiveness

The company generated K-M PFS and OS survival curves using pooled PFS and OS failure times from the latest data-cuts from the COMBI-d (January 2015) and COMBI-v (March 2015) trials. Failure times for vemurafenib OS were from data which had been adjusted for treatment switching in the 6% of patients who were initially randomised to vemurafenib but who switched to receive the trametinib+dabrafenib combination before the end of trial follow up.

Progression-free survival

The company used K-M data to model survival in each arm until a pre-determined breakpoint, beyond which a long-term linear trend was evident. The exact point at which the change in hazard occurred was estimated using the SiZer package (part of the R data analysis software).

Overall survival

The company employed K-M data until a pre-determined breakpoint, which was identified using the R software SiZer package. Beyond the breakpoint an assumption of constant hazards was utilised until year 5, after which it was assumed that mortality rates would converge with those from the American Joint Committee on Cancer (AJCC) Melanoma Registry[4] (case-mix adjusted). Beyond 20 years, age- and gender-matched general population mortality rates were added to AJCC mortality

rates to account for the increased risk of death in the metastatic melanoma population versus the general population (i.e. preserving a residual increased mortality and not assuming a cure).

5.3.6 Health-related quality of life

Health related quality of life data, using the EQ-5D 3L[48] tool, were collected as part of the COMB-d and COMBI-v trials at baseline and every 8 weeks thereafter through to week 56 and then every 12 weeks until progression. Assessments were also performed at the time of disease progression and 5 weeks post-progression. The company's approach is to assume that quality of life differs depending on health state (PFS or PPS) but is constant over time for that state. Utility during the PFS state differs depending on treatment. A single utility value has been used to represent quality of life in the PPS state. The utility values used in the company model are presented in Table 16.

Table 16 Utility values used in base case model

Health state	Treatment	Mean	Source
PFS	Trametinib+dabrafenib	0.837	Weighted average of all pre-progression utility assessments (excluding baseline) among trametinib+dabrafenib patients in pooled dataset
	Vemurafenib	0.746	Calculated based on estimated utility for trametinib+dabrafenib (0.8369) and difference in weighted average of all pre-progression utilities assessments (excluding baseline) for vemurafenib vs trametinib+dabrafenib in COMBI-v (-0.0908)
	Dabrafenib	0.789	Calculated based on estimated utility for trametinib+dabrafenib (0.8369) and difference in weighted average of all pre-progression utilities assessments (excluding baseline) for dabrafenib vs trametinib+dabrafenib in COMBI-d (-0.0479)
PPS		0.697	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

PFS=progression-free survival; PPS=post-progression survival
Source: CS, Table 86

The company carried out a systematic review to identify the humanistic burden among patients receiving first- or second-line treatment for metastatic melanoma (see CS Appendix 8.11 for the search strategy). Only two studies, the COMBI-d and COMBI-v trials, were identified.

5.3.7 Disutility associated with adverse events

The utility values used in the model have been derived directly from data collected as part of the COMBI-d and COMBI-v trials and, as such, they take into account the negative quality of life associated with any AEs.

5.3.8 Resources and costs

Therapy costs

Therapy costs are displayed in Table 17. It is assumed that each prescription will be for a 28-day supply of the medicine and that any unused medicine for patients who discontinue treatment during that 28-day period will be discarded.

A dispensing cost of £13.60 is assumed to be associated with each prescription. This is based on the assumption that it will take a hospital pharmacist (hourly rate £68.00)[65] 12 minutes to dispense the prescriptions.

Table 17 Cost of medication (list prices)

Regimen	Drug	Daily dose	Pack price	Unit price	Cost per dose	Cost per 28 days
Trametinib+ dabrafenib combination	Dabrafenib (75mg capsule)	300mg	£1,400* (28-capsule pack)	£50.00 per capsule	£200	£5,600
	Trametinib (2mg tablet)	2mg	£4,800† (30-tablet pack)	£160.00 per tablet	£160	£4,480
Dabrafenib monotherapy*	Dabrafenib (75mg capsule)	300mg	£1,400* (28-tablet pack)	£50.00 per capsule	£200	£5,600
Vemurafenib Monotherapy*	Vemurafenib (240mg tablet)	1920mg	£1,750* (56-tablet pack)	£31.25 per tablet	£250	£7,000

†CS
*BNF prices[63]
Cap=capsule; tab=tablet
Source: CS, Table 87 and Table 88

Relative dose intensity

Within the model it is assumed that patients are treated until progression. The amount of medication and the number of drug administrations are calculated based on the planned dose and the distribution of patients in the PFS state. However, the amount of medication and number of drug administrations may vary due to dose reductions, treatment interruptions and differences between time to treatment discontinuation and time to progression. The model includes relative dose intensity (RDI) multipliers to account for these differences (Table 18).

Table 18 Relative dose intensity multipliers used in the base case

Therapy		Relative dose intensity		Source
		Medication	Administration	
Trametinib+ dabrafenib	Dabrafenib	0.92	1.01	Analysis based on trametinib+dabrafenib combination data from pooled dataset (COMBI-d and COMBI-v)
	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)

RDI=relative dose intensity
Source: CS, Table 89

Health state unit costs and resource use

The company has used the same resource elements and utilisation rates as were used in the model considered in the appraisal of the use of ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268[10]), but has applied more up to date costs.[65,66] Costs used in the company model are summarised in Table 19 and full details are presented in Appendix 8.17 of the CS.

Table 19 Summary of resource use costs

Category	Cost	One-off or per cycle?	Source
Treatment initiation	£400	One-off	TA268[10]
PFS costs (outpatient visit [GP and plastic surgeon], inpatient stay, laboratory tests, radiological exams)	£148	Per cycle	TA268[10] and NHS Reference Costs 2013-14[66]
PPS (outpatient visit [largely medical oncologist], inpatient stay, laboratory tests, radiological exams)	£390	Per cycle	TA268[10] and NHS Reference Costs 2013-14[66]
Terminal care - applied on death	£7,287	One-off	Georghiou 2014[67]

PFS=progression-free survival; PPS=post-progression survival; GP=general practitioner
Source: CS, Table 91 and Table 92

Adverse event costs

Grade 3+ AEs experienced by 5% or more of patients in either the COMBI-d trial (January 2015 data-cut) or COMBI-v trial (March 2015 data-cut) are included in the company model. The incidences of events associated with treatment with the combination therapy were estimated using a weighted pooling of the incidences across the two trials. The incidence of AEs associated with treatment with dabrafenib (vemurafenib) monotherapy was estimated by applying the relative risk of each event from COMBI-d (COMBI-v) to the incidence of that event for the combination in the pooled dataset. The costs of treating the AEs were calculated by multiplying the

incidence of treatment-related AEs by the expected costs of these events. Risk of adverse events and associated costs are presented in Table 20.

Table 20 Adverse events – risks, relative risks and costs

Adverse event	Trametinib+ dabrafenib	Dabrafenib	Vemurafenib	Mean cost per patient	Source
	Risk (%)	Relative risk vs combination			
Hypertension	11.81	0.61	1.07	£1,438	Assumed to include an outpatient visit to a medical oncologist (Currency code 370-Consultant led: Follow up attendance non-admitted face to face, NHS Reference Costs 2013-14[66]) Half of the hypertension cases were assumed to be hospitalised
Rash	0.54	10.03	10.03	£363	Based on cost-of-illness study performed by INC Research (updated to NHS Reference Costs 2013-14[66])
Squamous cell carcinoma (SCC)	1.79	10.43	10.43	£1,308	
Keratoacanthoma	0.54	17.55	17.55	£1,308	Assumed to have the same cost as Grade 3+ SCC
Pyrexia	5.55	0.13	0.13	£1,160	Assumed to include an outpatient visit to a medical oncologist (Currency code 370-Consultant led: Follow up attendance non-admitted face to face, NHS Reference Costs 2013-14[66]) All cases of pyrexia were assumed to be hospitalised (see CS, Appendix 8.18 for calculation)
Basal cell carcinoma	2.15	0.5	0.5	£1,308	Assumed to have the same cost as Grade 3+ SCC INC Research[68]

Source: CS, Table 94, Table 95 and p214

Post-study anti-cancer treatment (PSACT) costs

The company has incorporated PSACTs into the PPS state. Expected PSACT costs per patient were estimated as a weighted sum of the expected total PSACT cost per patient progressing in the COMBI-d and COMBI-v trials. Details of the company's calculations may be found in Appendix 8.19 of the CS. The expected costs of PSACTs per patient over the lifetime are presented in Table 21.

Table 21 Expected mean PSACT cost per patient in the base case model

Therapy	Cost per patient	
	Mean	SE
Trametinib+dabrafenib	£55,220	£13,805
Vemurafenib	£65,002	£16,251
Dabrafenib	£69,617	£17,404

SE=standard error: PSACT=post-study anti-cancer therapy
Source: CS, Table 96

5.3.9 Model validation

The company states that the MS Excel model used in this appraisal is an adaptation of one that has been used in several prior economic evaluations (UK, Australia and Canada). The company who developed the model validated it by taking the inputs to the model and entering them into a different model, developed by a different analyst. The model was also checked and validated by investigators working for a different consultancy company. A third consultancy company also validated the model.

5.3.10 Results included in company submission

Predicted (per patient) effectiveness and costs generated by the company model are presented in Table 22.

Table 22 Summary of predicted efficacy and resource use by category of cost

	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
QALYs	3.443	2.098	2.146	1.345	1.298
Costs (discounted)					
Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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 QALY				**96,437**	**104,069**

QALY=quality adjusted life year
Source: CS, Table 100

When trametinib+dabrafenib therapy is compared with dabrafenib (Table 23) it leads to a lifetime increase in cost to the UK NHS of £135,058 per patient. In addition, it offers an additional 1.653 life years and 1.298 QALYs per patient. The resultant ICER for this comparison is £104,069 per QALY gained.

Table 23 Cost effectiveness results for the comparison of trametinib+dabrafenib with dabrafenib monotherapy (list prices)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/QALY)
Dabrafenib	[redacted]	2.933	2.146				-
Trametinib+ dabrafenib	[redacted]	4.586	3.443	£135,058	1.653	1.298	£104,069

Inc=incremental; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, Table 101

When trametinib+dabrafenib therapy is compared with vemurafenib (see Table 24) it leads to a lifetime increase in cost to the UK NHS of £129,707 per patient. In addition, it offers an additional 1.653 life years and 1.345 QALYs per patient. The resultant ICER for this comparison is £96,436 per QALY gained.

Table 24 Cost effectiveness results for the comparison of trametinib+dabrafenib with vemurafenib monotherapy (list prices)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/QALY)
Vemurafenib	[redacted]	2.933	2.098				
Trametinib+ dabrafenib	[redacted]	4.586	3.443	£129,707	1.653	1.345	£96,436

Inc=incremental; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, Table 101

The company's base case incremental cost effectiveness results (see Table 25) show that dabrafenib is cheaper than vemurafenib and its use results in a higher number of quality adjusted life years.

Table 25 Base case incremental cost effectiveness results (list prices)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER versus baseline (QALYs)	ICER (£/QALY)
Dabrafenib	[redacted]	2.933	2.146				-	-
Vemurafenib	[redacted]	2.933	2.098	£5,351	0.000	-0.047	Dominated	Dominated
Trametinib+ dabrafenib	[redacted]	4.586	3.443	£129,707	1.653	1.345	£104,069	£104,069

Inc=incremental; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, Table 101

5.3.11 Sensitivity analyses

Deterministic sensitivity analyses

The company carried out a wide range of deterministic sensitivity analyses. Resultant ICERs per QALY gained were generated using the 5% and 95% confidence interval values for the variables (except where indicated otherwise). The ICERs per QALY gained for the ten most influential parameters for the comparison trametinib+dabrafenib compared with dabrafenib and vemurafenib in Table 26 and Table 27 respectively. In each case the two most influential parameters are the model time frame and the assumption that there is not continuing benefit for PFS.

Table 26 Results from the seven most influential sensitivity analyses (trametinib+dabrafenib vs dabrafenib)

Parameter	Parameter adjustment		Difference between lower and upper bounds
	Lower	Upper	
Base case value: £104,069 per QALY gained			
Model timeframe (40-20 years)	£101,951	£114,550	£12,599
No continuing benefit assumed for PFS	£91,807	£104,069	£12,262
Utility decrement of PPS vs PFS (95% CI)	£102,373	£106,054	£3,681
PPS cost per month (±50%)	£102,294	£105,844	£3,550
PFS cost per month (±50%)	£103,613	£104,525	£912
Utility decrement of PFS vs perfect health (95% CI)	£103,746	£104,297	£551
Terminal care cost per month (±50%)	£103,885	£104,252	£367

CI=confidence interval; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year
Source: CS, Figure 42

Table 27 Results from the seven most influential sensitivity analyses (trametinib+dabrafenib vs vemurafenib)

Parameter	Parameter adjustment		Difference between lower and upper bounds
	Lower	Upper	
Base case value: £96,437 per QALY gained			
No continuing benefit assumed for PFS	£84,492	£96,437	£11,945
Model timeframe (40-20 years)	£94,555	£105,718	£11,163
PPS cost per month (±50%)	£94,724	£98,150	£3,426
Utility decrement of PPS vs PFS (95% CI)	£94,920	£98,212	£3,292
PFS cost per month (±50%)	£95,997	£96,877	£880
Terminal care cost per month (±50%)	£96,260	£96,614	£354
Utility decrement of PFS vs perfect health (95% CI)	£96,277	£96,583	£306

CI=confidence interval; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year
Source: CS, Figure 43

Scenario analysis

One scenario analysis was undertaken to explore the underlying assumption that trametinib+dabrafenib therapy continues to deliver benefit in the PFS state beyond the study follow-up period. In the base case, the continuing benefit assumption is implemented by assuming that the hazard for PFS in the combination arm is constant throughout the projection period. In the scenario analysis it is assumed that the monotherapy exponential projection applies to the combination arm from the end of follow-up. Results are displayed in Table 28.

Table 28 Scenario analysis – incremental results (list prices)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER versus baseline (QALYs)	ICER (£)/(QALY)
Dabrafenib	[redacted]	2.933	2.146	-	-	-	-	-
Vemurafenib	[redacted]	2.933	2.098	£5,351	0.000	-0.047	Dominated	Dominated
Trametinib+ dabrafenib	[redacted]	4.586	3.422	£111,867	1.653	1.324	£91,807	£91,807

ICER=incremental cost effectiveness ratio; LYG=life year gained; QALY=quality adjusted life year; Inc=incremental
Source: CS, Table 110

Probabilistic sensitivity analyses

The company undertook PSA to derive the mean ICER per QALY gained. List prices were used and the analyses were carried out using 1000 iterations of the cost effectiveness model. Results were broadly consistent with base case results (see Table 29).

Table 29 Probabilistic sensitivity analysis results (list prices)

	Base case results	PSA results		
Trametinib+dabrafenib combination		**Mean ICER**	**Lower 95% CI**	**Upper 95% CI**
Versus vemurafenib	£96,437	£101,332	£88,720	£141,247
Versus dabrafenib	£104,069	£109,380	£93,860	£159,250

CI=confidence interval; ICER=incremental cost effectiveness ratio; PSA=probabilistic sensitivity analysis
Source: CS, Section 5.8.3

The cost effectiveness plane and cost effectiveness acceptability curve (CEAC) for the pairwise comparisons are shown in Figure 4 and Figure 5 respectively. The CEAC shows that the probability of trametinib+dabrafenib combination being cost effective compared with either dabrafenib or vemurafenib at a threshold of £50,000 per QALY gained is 0% in both cases.

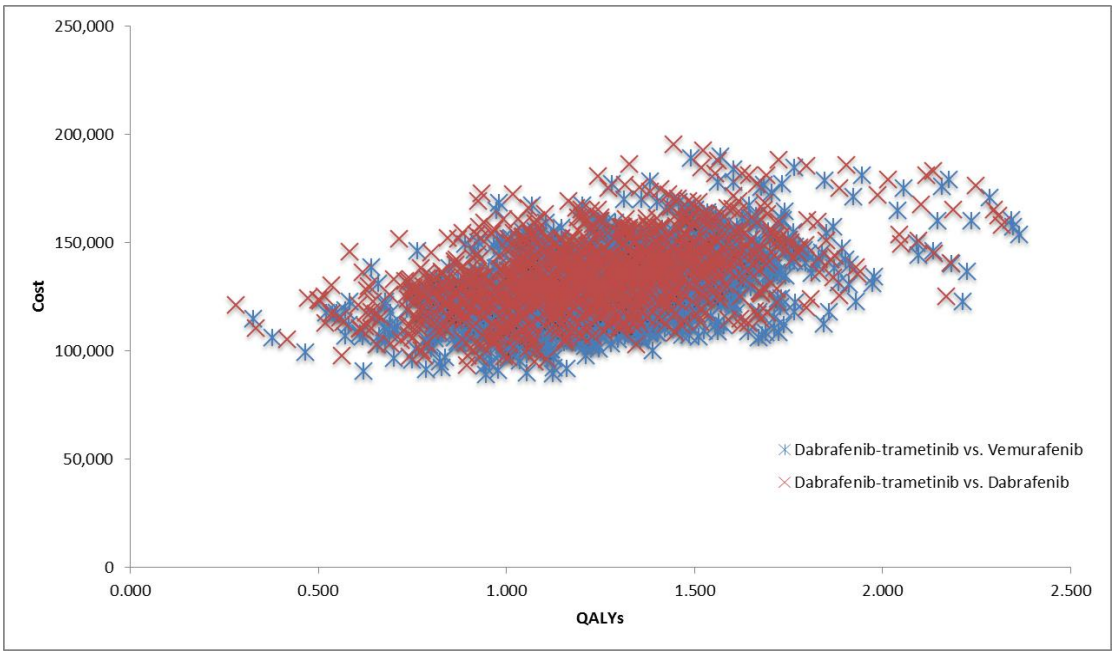

Figure 4 Scatterplot of PSA results

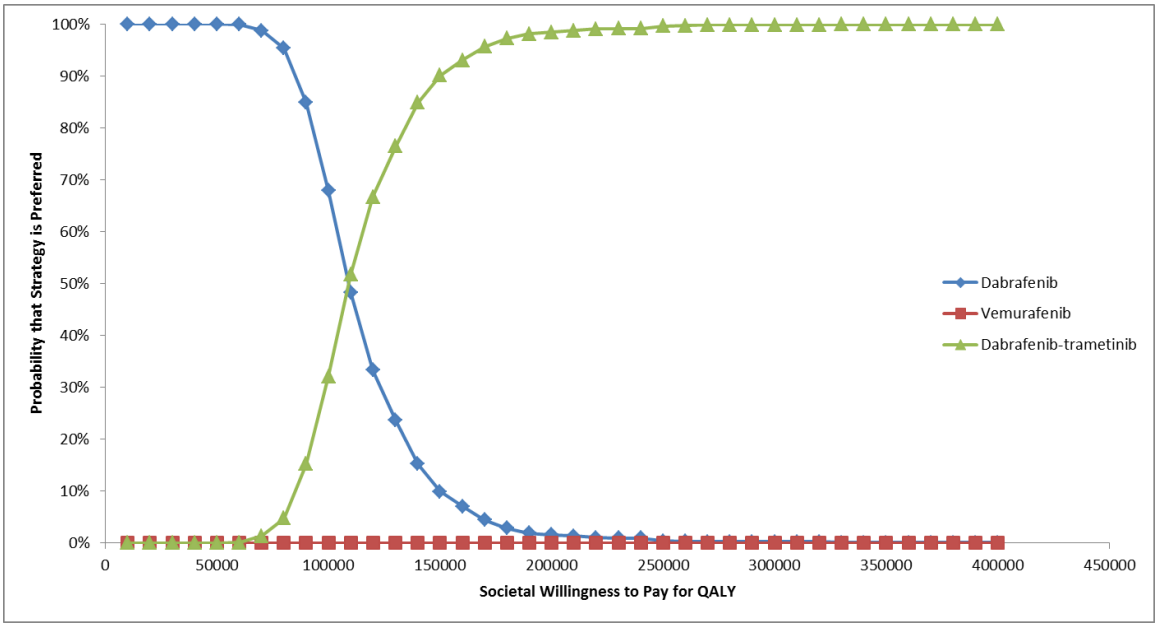

Figure 5 Incremental cost effectiveness acceptability curve

5.4 Summary and critique of company's submitted economic evaluation by the ERG

Table 30 NICE Reference case checklist completed by ERG

Attribute	Reference case[64]	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Patient related direct health effects are considered. No impact on carers has been considered in the model
Perspective on costs	NHS and PSS	Partial. The model only includes NHS costs. Personal Social Service costs have not been considered
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Cost effectiveness analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 30 year time horizon
Synthesis of evidence on health effects	Based on systematic review	No
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs and the EQ-5D instrument has been used to collect HRQoL data
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes - HRQoL data were collected as part of the COMBI-d and COMBI-v trials
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	No. The utility values were predominantly drawn from a non-UK (including US) patients
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes - NHS costs, valued at relevant prices, have been used
Discounting	The same annual rate for both costs and effects (currently 3.5%)	Benefits and costs have been discounted at the 3.5% rate

HRQoL=health related quality of life; PSS=Personal and Social Services; QALY=quality adjusted life year

5.4.1 Drummond checklist

Table 31 Critical appraisal checklist for the economic analysis completed by ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	The effectiveness of trametinib+dabrafenib was established for the period over which trial data are available. However, the long-term impact of this therapy is unclear
Were all the important and relevant costs and consequences for each alternative identified?	Partial	The ERG considers that the company should have included more detail relating to adverse events in their model
Were costs and consequences measured accurately in appropriate physical units?	Partial	The ERG revised the following parameter estimates in the company's model: OS, utility values, treatment costs and PSACT costs
Were the cost and consequences valued credibly?	Partial	The values used in the company model for AE costs and monitoring costs appear credible. However the ERG was unable to replicate the calculations carried out to derive these costs
Were costs and consequences adjusted for differential timing?	Yes	However, discounting was applied weekly rather than annually
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Partial	Deterministic and probabilistic sensitivity analyses were undertaken. Further scenario analyses were required to test the key assumptions in the model
Did the presentation and discussion of study results include all issues of concern to users?	No	Key scenario analyses were not undertaken and therefore the results were not presented

ERG=evidence review group; OS=overall survival; PSACT=post-study anti-cancer therapy; TTD=time to treatment discontinuation

5.5 Critique of company model and ERG additional analyses

5.5.1 Overview

The company model was built in Excel. It is poorly designed, difficult to navigate and the cost effectiveness results are awkward to generate. The ERG identified a flaw in the model design that casts doubt on the size of any of the ICERs per QALY gained generated by the model, both in the company base case and after ERG amendments. Rectifying the flaw would require extensive reconstruction, a task which is beyond the remit of the ERG.

In terms of the parameters chosen to populate the model, the ERG has a substantive concern about the way OS has been modelled for patients receiving a BRAF inhibitor monotherapy and the impact this has on the size of the company's estimated ICERs. The ERG also has significant concerns about the cost and utility values that the

company has used. Even when these concerns are addressed, the ERG considers that the structural flaw in the model means that results should be interpreted with caution.

The ERG also considers that the model does not represent the current treatment pathway for patients with advanced (unresectable or metastatic) melanoma who have progressed following treatment with a BRAF inhibitor.

5.5.2 Model structure and design

Modelling survival

The company model comprises three health states: progression-free, progressed and dead. The mortality rate is dependent on time and treatment arm, and is independent of progression state. The progression state (progression-free or progressed) only influences the cost of treatment and utility.

As the company points out, this model structure is the same as that employed in previous NICE STA submissions in this disease area, most recently in the appraisal of pembrolizumab for treating ipilimumab naïve unresectable, metastatic melanoma.[15] In the most recent NICE appraisal[15] of pembrolizumab, the ERG criticised the model structure as the cost effectiveness results generated by the model showed that, as the effectiveness of pembrolizumab (measured in terms of delaying progression) decreased, cost effectiveness increased. The ERG considers that an appropriate model structure would generate cost effectiveness results that show that a reduction in the efficacy of the intervention leads to an increase in the size of the ICER in respect of the comparator.

This counterintuitive finding is also found in the company model for this appraisal. The issue is exemplified by the scenario analysis undertaken by the company in which the hazard ratios for progression at the end of the trial period are assumed to be equal for both the trametinib+dabrafenib arm and the dabrafenib monotherapy arm, rather than lower for the trametinib+dabrafenib arm as in the company base case analysis. This assumption effectively makes treatment with trametinib+dabrafenib less effective at delaying progression than in the company base case analysis. However, in this scenario, the model generates an ICER for trametinib+dabrafenib treatment compared to monotherapy that is lower than the ICER in the company base case analysis (see CS, Table 101 and Table 110).

This result can be explained by looking at the scenario analysis results in detail – specifically at the changes in costs, LYG and QALYs.

As the progression state is independent of mortality, changing the hazard for progression in the trametinib+dabrafenib arm does not alter OS for patients receiving that therapy. It merely changes the proportion of time patients remain in the progression-free state. This is seen in the company scenario analysis results where LYG from treatment with trametinib+dabrafenib therapy compared to monotherapy remain the same (1.653 years) as LYG for the same comparison in the company base case.

In the company's scenario analysis, the difference in time in the progression-free state between treatment with trametinib+dabrafenib and monotherapy decreases from 0.667 years in the company base case to 0.517 years. As progression is linked directly to time on treatment, the mean difference in cost between trametinib+dabrafenib therapy and dabrafenib monotherapy decreases from £135,058 in the company base case to £117,217 in the scenario analysis (a cost reduction of 13.2%). Similar decreases are seen in the comparison of trametinib+dabrafenib therapy with vemurafenib monotherapy.

Compared with the company base case, the scenario analysis predicts less time in the progression-free state for patients receiving trametinib+dabrafenib. Time in the progression-free state is associated with a higher utility than the progressed state. Results from the scenario analysis, therefore, predict that there will be a reduction in QALYs for patients treated with trametinib+dabrafenib even though the total LYG remains the same as in the company base case analysis. Specifically, the QALY gain from treatment with trametinib+dabrafenib in the scenario analysis falls by 0.021 or 1.6%.

A 13.2% fall in costs and a 1.6% fall in QALYs explains, mathematically, why the ICER in the scenario analysis is lower than the ICER in the company base case analysis and highlights either that it is the failure to link progression state with differential mortality rates that leads to illogical model results or that the progression-free state as described is not a useful state to include in the economic model.

Effectively, the model structure makes it impossible to explore how changes in the assumption of the effectiveness of treatment with trametinib+dabrafenib at delaying or stopping progression impact on the size of the ICERs. The ERG has partially

addressed this issue by using time to treatment discontinuation (TTD) data rather than PFS as the basis for estimating costs and utilities, but the problem still essentially remains.

Patient pathway

The company model only relates to patients who receive a BRAF inhibitor as first-line therapy. However, the treatment pathway in the company model fails to reflect current clinical practice post progression.

Details provided in the CS on the PSACTs of patients included in the COMBI-d and COMBI-v trials show that, in any arm of both trials, fewer than 7% of patients received pembrolizumab and only 29% received ipilimumab post progression. The ERG considers that this does not reflect current clinical practice in the NHS where it would be expected that most, if not all, patients who well enough to start a second line-therapy would be offered pembrolizumab. This failure to incorporate second-line treatment with pembrolizumab in the company model casts doubt on the OS estimates presented by the company (and those produced by the ERG).

Furthermore, it is stated within the COMBI-d and COMBI-v trial protocols that patients who continue to receive study treatments after disease progression (125 patients in the COMBI-d trial and 183 patients in the COMBI-v trial) should be informed of the treatment options that they are forgoing and be provided with information on the effectiveness of these treatments. Given the information now available on the efficacy and tolerability of pembrolizumab, as well as the NICE recommendations[14,15] for its use, the ERG considers that it is likely that if patients in the COMBI-d and COMBI-v trials had been presented with the option of receiving pembrolizumab at the time of disease progression then more patients would have chosen to switch from their study treatment to receive pembrolizumab.

The potential impact of pembrolizumab on patients' choice to switch treatment at the time of disease progression and the resultant impact on survival should be considered when interpreting the model survival and economic results.

5.5.3 Overall survival

In the company model, OS K-M trial data from the COMBI-d and COMBI-v trials are used for the 30 months for which data are available. Using these data the difference in mean life years gained from treatment with trametinib+dabrafenib compared to BRAF inhibitor monotherapy is calculated to be 0.235 years. This compares to a gain

from trametinib+dabrafenib treatment of 1.653 years generated by the company model over 30 years. This means that 85.3% of the survival gain in the company model from trametinib+dabrafenib treatment is generated by assumptions on how to extrapolate the K-M data over the 30 year model time horizon. Therefore, in terms of the validity of model results, the most important assumptions that the company makes are those that influence OS projections.

The company states that they adopt a four-phase approach to projecting OS:

- K-M OS data are used directly until a 'breakpoint' is identified, this point differentiates between the initial period during which the mortality hazard is unstable and a later period in which the mortality hazard is considered to be constant
- Application of the constant mortality hazard until year 5, at which point the hazard converges with hazard rates from 5 years onwards from the AJCC registry data[4]
- Use of the AJCC registry data mortality hazard from year 5 until year 20
- Population mortality adjusted by an additional risk of mortality multiplier of 1.4 (CS, p199) for patients with melanoma from year 20 to year 30.

The ERG has a number of concerns about how the available data are included in the model, as well as the approach to extrapolation adopted by the company. These issues cast doubt on the validity of the ICERs generated in the company base case.

Censoring method

As part of the clarification process the ERG requested that the K-M analyses for OS be reproduced using the ERG's preferred method of censoring, whereby patients are assumed to remain alive until the end of the data collection period in the absence of evidence to the contrary, rather than to the time of the last observation. The company's response to the clarification request included a lengthy discussion of the relative merits of both approaches in different circumstances, including recognition that the relative magnitude of bias associated with the two approaches cannot be quantified. The company then took a decision not to fulfil the ERG's request and did not provide the data in the manner requested.

The ERG acknowledges that bias can occur when using either censoring method. However, the ERG considers that the potential impact of the bias in the company approach should be explored by analysing data obtained using the ERG's preferred approach. Due to time constraints the ERG took the decision to re-request only a subset of the data asked for in the original clarification letter. The ERG informed NICE and the company that, to be useful, the re-requested data would have to be

made available to the ERG before or on a specified date. However, these data were not provided to the ERG by that deadline and so the ERG was unable to carry out their intended analyses.

Pooling of OS data from COMBI-d and COMBI-v trials

As concluded in Section 4.11 the ERG considers that it was inappropriate to use pooled OS data from the COMBI-d and COMBI-v trials in the economic analyses.

The COMBI-d trial was a blinded and placebo controlled trial, whilst the COMBI-v trial was an open-label trial that did not involve a placebo. The methodology employed in the COMBI-d trial is, therefore, considered to be “gold standard”, whilst the method used in the COMBI-v trial is recognised as having limitations and being prone to potential biases. For example, the placebo effect from trametinib+dabrafenib therapy was not accounted for in the COMBI-v trial, whereas it was accounted for in the COMBI-d trial.

The ERG has concerns that the method used by the company to pool OS data fails to take any account of potential trial design bias. The PSA carried out by the company used bootstrapping; however, this was in recognition of potential differences in baseline patient characteristics, rather than concern about any potential trial design bias. The ERG is unaware of any methods that could be employed to account for unknown bias when pooling a dataset to produce unbiased K-M curves, and the company did not suggest a method.

As shown in Figure 6, the OS K-M curves generated using data from the COMBI-d and COMBI-v trials are essentially identical for the trametinib+dabrafenib arms of both trials. However, the same figure shows that there is a clear difference in OS between dabrafenib (COMBI-d) and vemurafenib (COMBI-v) from about month 17 to the end of the period for which K-M data are available, at which point 4% more patients in the dabrafenib arm are alive. By pooling OS data from the COMBI-d and COMBI-v trials for patients receiving BRAF inhibitor monotherapy, the company model provides a lower estimate of OS for these patients than if data from only the COMBI-d trial had been used.

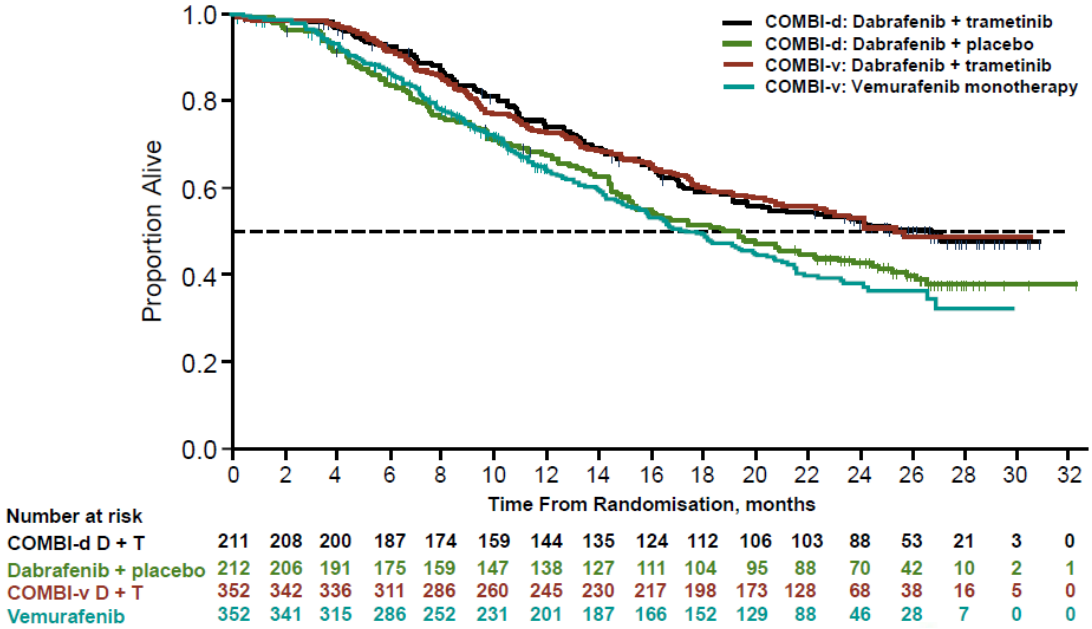

Figure 6 K-M curves for the COMBI-d and COMBI-v trials

Source: CS, Figure 26

Given the superior trial design of the COMBI-d trial, most notably in being able to take into account the placebo effect of treatment with trametinib+dabrafenib, the ERG considers that an analysis using only COMBI-d data would produce a more realistic ICER for trametinib+dabrafenib compared to both dabrafenib and vemurafenib monotherapies (on the assumption that dabrafenib and vemurafenib are equally effective at extending survival).

Use of AJCC registry data

The company makes use of the AJCC registry data in its extrapolation of OS. The ERG considers that, in the absence of an obviously better alternative, this is an acceptable approach. However, the weaknesses of the AJCC data and the way the data have been incorporated into the model need to be carefully considered when interpreting the cost effectiveness results generated by the model, namely:

- The AJCC registry data were collected over a period of time when treatments for melanoma were limited and largely ineffective. Today, a number of treatments are available for patients with advanced (unresectable or metastatic) malignant melanoma and, therefore, projections based on the experience of patients included in the AJCC data set may be unduly pessimistic. Immunotherapies are now available to NHS patients and their use is likely to impact on life expectancy in this population, an impact that is not captured by the AJCC data. Use of the AJCC data is, therefore, likely to underestimate the gain in life, at any stage in the disease trajectory, for both patients treated with trametinib+dabrafenib and those treated with a BRAF inhibitor monotherapy.

- The survival curves generated from the AJCC data cover the period from the time of initial melanoma diagnosis and reflect staging at time of diagnosis. To use AJCC data to generate a survival curve for a specific population, the data must be adjusted by the time since diagnosis and melanoma stage. Whilst the company adjusted for the case mix (age, sex and stage) of patients included in the COMBI-d and COMBI-v trials, no adjustment was made for the time since diagnosis.

As data on the time since disease diagnosis are not available, the ERG could not adjust the time point at which AJCC data should have been applied in the company extrapolation of OS.

The monthly mortality hazard rate in the AJCC data (adjusted for the case mix of patients included in the COMBI-d and COMBI-v trials) falls over time so that, at 5 years, it is 1.1% compared to 0.8% at 6 years. The lack of adjustment for time since diagnosis before application of the AJCC registry data has, therefore, potentially underestimated survival for all patients, independent of whether they receive trametinib+dabrafenib or dabrafenib.

The ERG re-ran the company base case model shifting the point at on the AJCC survival curve at the time when the mortality hazard rate is applied in the company model by 12 months. This made a negligible difference to the size of the ICER (less than 1%). So, whilst the company has used the AJCC registry data slightly inaccurately by failing to adjust for time since diagnosis, it does not appear that this has an important impact on cost effectiveness results, even in the unlikely event that treatment had been delayed by a full year following diagnosis.

The company extrapolated the AJCC registry data from year 10 to year 20. The ERG explored alternative approaches to extrapolation over this time period and found that their alternatives made less than a 2% difference to the size of the resultant ICERs. The ERG therefore took the pragmatic decision not to implement any adjustments.

Extrapolation over the period during which K-M data are available

The company identified a breakpoint in the trametinib+dabrafenib and BRAF inhibitor monotherapy K-M curves after which constant morality hazards were observed. This breakpoint was 18 months for trametinib+dabrafenib treatment and 3 months for BRAF inhibitor monotherapy. After this breakpoint a constant mortality hazard was applied even though K-M data were still available.

The ERG considers that, unless there are compelling reasons not to use all of the data available from a trial, it is preferable to incorporate the trial evidence as it is

rather than extrapolate over the period for which data are available. As such, the ERG amended the model by using the K-M data directly (but separately) from the two arms of the COMBI-d trial over the first 27 months. After 27 months there were no further deaths recorded in either arm of both trials, the only events being censoring events.

Extrapolation from the breakpoint until 5 years

On checking the company model, the ERG identified that the second projection phase was not as described in the CS. The constant mortality hazard identified at the breakpoint was not applied until year 5 as stated by the company, but only until month 30 for trametinib+dabrafenib therapy and month 31 for BRAF inhibitor monotherapy (these time points approximately match the duration of available follow up data). The monthly mortality hazard in both arms then decline at a constant rate to converge with the mortality hazard at 5 years, which was derived from the AJCC registry data. From 5 years, the monthly mortality hazard is assumed to match the mortality hazard from year 5 in the AJCC registry data each month to year 20 regardless of treatment arm.

Examination of the survival curves produced by the company, compared to the survival data from the COMBI-d and COMBI-v case mixed adjusted AJCC registry data (Figure 7), shows that fewer patients are alive at year 5 in the BRAF inhibitor monotherapy arm (14.0%) than would be predicted by the AJCC data (14.2%).

The ERG considers this implausible, especially given the issues raised earlier in this report about the AJCC registry data probably overestimating the underlying mortality for the patient groups in the COMBI-d and COMBI-v trials at all time points during the trial.

This counterintuitive result is directly attributable to the constant mortality hazard rates applied by the company both during the period where K-M data were available and up to year 5.

[redacted]

Figure 7 Company projected OS to 5 years compared with the AJCC registry data survival curve

From 3 months the company applied a mortality hazard rate for BRAF inhibitor monotherapy of 4.4%. Whilst the mortality hazard rate between months 3 and 4 suggested by the AJCC registry data is 7.0%, by month 14 the monthly mortality hazard has fallen to 4.3% and falls to 1.1% by month 60 (year 5 – when the mortality hazard rate for BRAF therapy converges with the AJCC registry mortality hazard in the company model). So for almost 4 years the monthly mortality hazard rate for BRAF inhibitor monotherapy is higher in the company model than for patients in the AJCC registry over the same time period.

For patients receiving trametinib+dabrafenib, the monthly constant mortality hazard is 2.3% from 18 months at which point the monthly mortality hazard in the AJCC registry is 3.4%. The monthly mortality hazard rate for the AJCC data at 30 months – the point at which the company has started to converge mortality hazard rates to the AJCC data – is 2.4%. The monthly mortality hazard for trametinib+dabrafenib, therefore, essentially converges with the AJCC registry data at 30 months rather than at 60 months and is always lower until the hazards converge at year 5.

Further evidence on the implausibility of such a large difference between monthly mortality hazard rates over 5 years is found in the post treatment discontinuation survival curves.

If treatment with trametinib+dabrafenib really does lead to a lower monthly mortality hazard over 5 years, given more than half the patients have stopped treatment in any arm of both trials by 12 months, it would be expected that treatment with trametinib+dabrafenib would confer a survival advantage over BRAF inhibitor monotherapy once treatment stopped. To explore this, the ERG asked for the company to provide K-M data from the COMBI-d trial on post treatment discontinuation survival. Only COMBI-d data were requested to avoid any bias in the decision to stop treatment due to knowledge of treatment arm by clinicians and patients that may have existed in the COMBI-v trial, due to the open-label nature of this trial.

The post treatment discontinuation K-M curves from the COMBI-d trial are shown in Figure 8 and provide evidence that post treatment survival is the same regardless of treatment with trametinib+dabrafenib or dabrafenib. If anything, patients in the dabrafenib arm appear to have improved post treatment survival compared to patients in the trametinib+dabrafenib arm, at least up until about 7 months.

[redacted]

Figure 8 Post treatment discontinuation survival from the COMBI-d trial

Source: Novartis response to additional clarification question (27 January 2016. Figure 1)

Given the implausibility of the company OS extrapolation for patients receiving a BRAF inhibitor monotherapy, the ERG determined that an alternative method of extrapolating OS beyond the point at which reliable K-M data from the COMBI-d and COMBI-v trials were available.

The average monthly mortality hazard rate from the pooled monotherapy arms of the COMBI-d and COMBI-v trials for patients receiving a BRAF inhibitor monotherapy was 3.1% for months 21 to 27. For the dabrafenib arm of the COMBI-d trial, over the same period, the average monthly mortality hazard was 2.4%. As stated, for trametinib+dabrafenib the company has identified a constant mortality hazard from 18 months of 2.3%. Given the monthly mortality hazard in the AJCC registry data is 2.5% at month 27, AJCC registry survival data could be applied from month 27 onwards for both the trametinib+dabrafenib and BRAF inhibitor monotherapy arms.

Extrapolation post 20 years

The company has assumed that, after 20 years, mortality for patients with melanoma is that of the general population uplifted by a factor of 1.4. The magnitude of the uplift factor reflects the difference in mortality hazard between general population mortality 20 years into the model when the population is age 75 and the mortality predicted by projection of the AJCC registry data at 20 years The ERG recognises that there is logic to this approach, but equally that it is an assumption that cannot be supported, or disputed, by the available data. However, only 7.7% of the estimated QALYs accumulated by patients treated with trametinib+dabrafenib, and 6.0% of those treated with either vemurafenib or dabrafenib, occur after 20 years. Thus, the assumption of increased mortality has an insignificant impact on the cost effectiveness results generated by the model.

ERG alternative approach to modelling OS

Based on the issues found in the company approach to estimating OS, the ERG considers that a number of modifications can be made to the OS projection that improve the accuracy of the ICERs per QALY gained generated by the company model. The ERG's approach is, namely:

1. Use of K-M data directly for trametinib+dabrafenib and BRAF inhibitor monotherapy until month 27 with no extrapolation during this period
2. Use of mortality hazard rates from AJCC data from month 27 to year 20
3. Population mortality adjusted by an additional risk of mortality multiplier (1.4) for patients with melanoma from year 20 to year 30 (same as in the company model).

The ERG also considers that data from the COMBI-d trial, rather than the pooled data from the COMBI-d and COMBI-v trials, provide a more robust estimate of the differential in OS that results from treatment with trametinib+dabrafenib compared with dabrafenib monotherapy.

The company OS projections and the ERG revised OS projections up to 5 years, are shown in Figure 9**.**

[redacted]

Figure 9 Company and ERG revised OS projections

As expected, the ERG revisions result in an OS projection that is very similar to the company projection of OS for trametinib+dabrafenib. Discounted life years with the ERG OS amendment, and using pooled data from the COMBI-d and COMBI-v trials, for trametinib+dabrafenib, fell slightly from 4.586 years to 4.511 years (4.562 years using only data from the COMBI-d trial).

For BRAF inhibitor monotherapy the difference that the ERG amendments makes is substantial. Using pooled data from the COMBI-d and COMBI-v trials, the mean discounted life expectancy increases from 2.933 years in the company model to 3.461 years and rises to 3.696 years when using data from the COMBI-d trial only.

The ERG's changes to OS increase the size of the ICER per QALY gained for trametinib+dabrafenib compared to dabrafenib from £104,069 in the company base case to £150,821 (£175,493 when using data from the COMBI-d trial only) and, compared to vemurafenib, from £96,436 to £137,373 (£158,430 when using data from the COMBI-d trial only).

5.5.4 Treatment costs

The ERG considers that the methods used by the company to calculate study treatment costs are inaccurate.

On-treatment costs

The ERG requested treatment data for patients who continued to receive study treatment post-investigator assessed progression (specifically more than 15 days post-progression, at which point continuation of treatment was considered to be deliberate). These data are shown in Table 32 and highlight that there is a substantial number of patients in both arms of both trials who continued to receive study treatment post progression. The mean time on treatment after progression is also noteworthy, being over 200 days (over 6 months) in the trametinib+dabrafenib arm of the COMBI-D trial. The ERG considers, therefore, that PFS is a poor proxy for time on treatment (and therefore treatment costs) and that TTD is a better proxy measure.

Table 32 Patients continuing on treatment post investigator-assessed progression in the COMBI-d and COMBI-v trials

	Percentage of patients who continued on study treatment post progression	**Days of study treatment post progression (mean [sd])**
COMBI-d trial		
Dabrafenib+trametinib	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]
COMBI-v trial		
Dabrafenib+trametinib	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]

sd=standard deviation

The ERG considers that differences in both the proportion of patients who continued on treatment in the two trials and the mean length of time patients continued with treatment are likely, in part, to be driven by the fact that the COMBI-v trial was not blinded. In addition, whilst TTD data from the trametinib+dabrafenib arms in the COMBI-d and COMBI-v trials are almost identical, TTD data for patients treated with vemurafenib and dabrafenib are markedly different, with only 26.9% of patients still on BRAF inhibitor monotherapy at month 12 in the COMBI-v trial, compared with 37.9% of patients in the COMBI-d trial.

The differences, shown by the data presented in Table 32, highlight how differential clinical and patient behaviour may lead to biased outcomes in open-labelled trials.

This adds weight to the argument supporting the use of data from the COMBI-d trial only for patient outcomes in the model.

The ERG considers that if dabrafenib and vemurafenib are equally clinically efficacious then the results from the dabrafenib arm of the COMBI-d trial can be applied equally to modelling the experience of patients receiving vemurafenib. Given this, and the potential bias present in the open-label COMBI-v trial, the ERG considers that only TTD results from the COMBI-d trial should be employed in the model. TTD data are available monthly up to 30 months. The cumulative hazards for the TTD data from both arms of the COMBI-d trial are shown in Figure 10.

[redacted]

Figure 10 TTD cumulative hazard data from the COMBI-d trial

Source: Novartis response to clarification question (Q1b, Table 1.5)

Only a small number of data points are available. This means that is difficult to ascertain whether the hazard has become constant at 30 months and to be confident that any curve can be fitted to the data. This issue is compounded by the end of the curves potentially being erroneous due to a relatively large reduction in the number of patients stopping trametinib+dabrafenib treatment.

In the COMBI-d trial, 29.4% of patients were on treatment at 29 months, falling to 23.8% at 30 months. The same reduction was not seen in the trametinib+dabrafenib arm of the COMBI-v trial, where between months 28 and 32 there was a fall from 29.1% to 27.5%. However, data for patient receiving dabrafenib suggests no patient

stopped treatment between 28 and 30 months despite there being a steady reduction in patients on treatment up to that point.

The ERG considers that the end of the TTD curves are likely to be influenced by censoring or to be the result of some artefact of the trial and that mortality hazard rates over the last few months of the trial may not be reliable. The ERG has, therefore, focussed only on the first 27 months of data and has extrapolated the TTD data by calculating the average mortality hazard rate in each arm from months 12 to 28 and applied this as a constant monthly hazard from month 28 onwards. This approach has resulted in a monthly mortality hazard for treatment discontinuation of 3.2% for patients treated with trametinib+dabrafenib and 5.6% for those treated with dabrafenib.

The TTD K-M curves and the extrapolation for trametinib+dabrafenib and dabrafenib, compared to the company estimated PFS for trametinib+dabrafenib and BRAF inhibitor monotherapy are shown in Figure 11.

[redacted]

Figure 11 ERG estimated TTD and company modelled PFS

The ERG considers that application of TTD only partially negates the need for the RDI (relative dose intensity) adjustment applied by the company. In Table 51 of the CS dose interruptions were shown for almost 50% of patients across both arms of the COMBI-d and COMBI-v trials and dose reductions due to AEs were noted for between 14% and 36% of patients. As such, some estimate of RDI would be

considered reasonable. The ERG did not request patient level data to recalculate the RDI based on TTD and so has applied the RDI used in the company base case.

The ERG re-ran the company model using TTD data instead of PFS data to estimate treatment costs. The results of the re-analysis show that mean total costs per patient for trametinib+dabrafenib increase from £[redacted] in the company base case to £320,153. Costs for dabrafenib increase from £[redacted] to £170,405 and for vemurafenib from £[redacted] to £176,803.

The ICER per QALY gained for trametinib+dabrafenib compared to dabrafenib increases from £104,069 in the company base case to £115,457 and, compared to vemurafenib, from £96,437 to £106,580.

The ERG considers that, in clinical practice, TTD is likely to be affected by the availability of pembrolizumab, and possibly ipilimumab, as treatment options. Patients may now choose to switch to immunotherapy and away from BRAF inhibitor therapy either because their individual treatment pathway was planned for them to take BRAF inhibitors until they were well enough to commence immunotherapy or because, on disease progression, they choose to commence immunotherapy rather than remain on a BRAF inhibitor, where this is an option. This means that both the company base case results and the ERG's results may overestimate the time on treatment on all arms and so overestimate costs. This is a further example of how the failure to represent the current treatment pathway casts doubt on any model outputs.

Post-study anti-cancer therapy costs

In the company model it is assumed that patients receiving first-line treatment with trametinib+dabrafenib have different PSACTs from those whose first-line therapy was a BRAF inhibitor. The company offered no justification as to why these costs should be different. No statistical tests were performed to support this assumption and the standard errors presented in Table 96 of the CS would suggest that PSACT costs between arms were not statistically significantly different.

Given the lack of clinical or statistical justification to apply different PSACT costs, a single PSACT of a simple average of the three expected mean PSACT cost per patient used in the company base case model (CS, p215) was used i.e. £63,280. The ERG has applied this cost at the end of treatment discontinuation as a one-off cost, rather than at progression as in the company model. The ERG considers that this cost should be spread across the duration of treatment to allow it to be appropriately

discounted. However, insufficient data are available to show how the data should be spread. Furthermore, even if it were possible, such an approach would be unlikely to have a large impact on the size of the ICER per QALY gained.

Application of a single PSACT cost regardless of treatment arm to the company base case increases the mean total costs per patient for patients treated with trametinib+dabrafenib from £[redacted] in the company base case to £305,706. Mean total costs per patient for those treated with dabrafenib decrease from £[redacted] in the company base case to £156,754, and total costs per patient for those treated with vemurafenib decrease from £[redacted] to £166,319. The resultant ICER per QALY gained for trametinib+dabrafenib compared to dabrafenib increases from £104,069 in the company base case to £114,843 per QALY gained and, compared to vemurafenib, increases from £96,436 to £103,633 per QALY gained.

The ERG considers that the PSACT costs should have been adjusted for PAS prices. However, the real issue is the difference in PSACT costs between the treatments and not the absolute cost. To exemplify this, if PSACT costs were set to zero for both the intervention and comparator treatment arms then the ICER per QALY gained or trametinib+dabrafenib compared to dabrafenib in the ERG re-analysis would be £115,388 rather than £114,744. As such, the failure to include PAS prices in the PSACT costs has a minimal impact on results generated by the ERG's re-analysis.

Whilst the ERG considers that the re-analysis of PSACT costs produces a more accurate ICER than the company base case, the ERG also considers that the data used from the COMBI-d and COMBI-v trials to estimate the PSACT costs is not representative of current clinical practice. Given that no more than 7% of patients in any arm of the COMBI-d or COMBI-v trials received pembrolizumab as a second-line treatment, the ERG considers this renders the company's PSACT costs out of date. Again, the outputs from the model (both company base case and ERG re-analysis) should be interpreted with caution due the model pathway not being representative of current clinical practice.

5.5.5 Utility estimates

European utility values

The NICE Reference Case[64] stipulates that utility values should be derived from UK patients. Only a small number (n=72) of UK patients participated in the COMBI-d and COMBI-v trials. As part of the clarification process, the ERG requested utility values for the UK and European patients included in the COMBI-d and COMBI-v trials at

different time points. The ERG considers that values from the subgroup of European patients would provide a more representative estimate of utility values for UK patients than the total dataset.

Dabrafenib versus vemurafenib

As was the case with TTD, the ERG considers the use of utility data from the COMBI-v trial to be inappropriate due to the open-label nature of the trial. Patient reported outcomes, such as quality of life, are likely to be biased by an open-label trial, a view supported by the European Medicines Agency in a workshop on HRQoL in oncology.[69]

In this case, for treatment with trametinib+dabrafenib and dabrafenib at least, utility evidence is available from a fully blinded trial (the COMBI-d trial) and so there is no need to introduce potential bias into utility estimates by using the open-label utilities from the COMBI-v trial.

For vemurafenib, the company data used data collected during the open-label COMBI-v trial. Whilst this evidence would appear to support the view that treatment with vemurafenib should be associated with a lower utility value than dabrafenib, it is noted that in previous NICE submissions, notably for dabrafenib first-line treatment, TA321[12] the same utility value was applied for dabrafenib and vemurafenib. The ERG is not convinced that the open-label nature of the COMBI-v trial is compelling evidence that the utility of patients receiving vemurafenib is lower than that for patients receiving dabrafenib. Even if it was the case that utility data from the COMBI-v trial were sufficiently robust, the evidence from the European dataset is that at no time point up to 56 weeks were the utility values from the vemurafenib arm of the COMBI-v trial statistically significantly different from those at the same time point from the dabrafenib arm of the COMBI-d trial (Table 33).

Table 33 Utility values for European patients treated with dabrafenib (COMBI-d) and vemurafenib (COMBI-v)

Time point	Dabrafenib			Vemurafenib			Difference in means
	n	Mean	sd	n	Mean	sd	
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n=number of patients; sd=standard deviation
*p<0.05
Source: Clarification response, QB3, Table 4.0105

As shown in

Table 33, not only are the utility values statistically insignificant at all time points, but also the treatment associated with the highest utility value varies in an apparently random manner. Given this, the ERG considers that there is no statistical basis to apply a different utility to the vemurafenib and dabrafenib arms of the model. Therefore, the same utility values are used for the two treatments, an approach that has been applied in a previous NICE STA.[12]

Trametinib+dabrafenib versus dabrafenib

To assess the potential difference in utility between trametinib+dabrafenib and dabrafenib, the ERG analysed utility values collected from European patients participating in the COMBI-d trial. The utility values collected up to week 56 of the trial are shown in Table 34.

Table 34 Utility values for European patients included in the COMBI-d trial

Time point	Trametinib+dabrafenib			Dabrafenib			Difference in means
	n	Mean	sd	n	Mean	sd	
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n=number of patients; sd=standard deviation
*p<0.05
Source: Clarification response, QB3, Table 4.0105

Table 34 shows that only in weeks 8, 16 and 40 was the difference in utility between arms statistically significant ($p<0.05$). The baseline mean utility, whilst not statistically significantly different between arms, is 0.023 higher in the trametinib+dabrafenib arm than in the dabrafenib arm. If the utility values post-baseline were adjusted for this difference then only the utility values at week 40 would be statistically significantly different between arms. The ERG does not consider, therefore, that a statistical argument for differential utilities for trametinib+dabrafenib compared to dabrafenib is compelling.

Whilst utility on treatment is not just driven by AEs, the ERG considers that the AE data from the COMBI-d trial for both arms does not equivocally demonstrate that treatment with trametinib+dabrafenib is more tolerable than treatment with dabrafenib. Results from the COMBI-d trial show that there were greater incidences of any AE, AEs leading to permanent discontinuation of study treatment, AEs leading

to dose reduction, AEs leading to dose interruption and fatal SAEs in the trametinib+dabrafenib arm than in the dabrafenib arm (CS, Table 51). These could all be expected to impact on quality of life, even if the symptoms were relatively mild and only classed as Grade1 or 2. For some AEs, notably rash and squamous cell carcinoma, patients in the trametinib+dabrafenib arm experienced more events than those receiving dabrafenib.

The ERG considers there is no AE evidence data to support a higher utility for patients receiving trametinib+dabrafenib than for those receiving dabrafenib. Furthermore, the evidence, notably on the higher likelihood of dose reduction and ceasing treatment for patients receiving trametinib+dabrafenib compared with those receiving dabrafenib, would seem to support the view that treatment with trametinib+dabrafenib is, on average, less tolerable and associated with a lower utility than treatment with dabrafenib. However, the ERG considers that the improved levels of response seen with trametinib+dabrafenib compared to dabrafenib may mitigate any reduction from increased AEs.

On balance, the ERG considers that there is no robust statistical or clinical evidence to support applying different utilities for treatment with trametinib+dabrafenib compared with treatment with dabrafenib. As the ERG also considers that dabrafenib treatment should be associated with the same utility value as treatment with vemurafenib, this means that the ERG considers that only one utility value should be applied whilst on study treatment, regardless of therapy.

PFS/PPS utility value

In addition to K-M PFS data being an unreliable basis for estimating treatment costs, the ERG also considers that K-M PFS data are a questionable basis for estimating utility. Utility measures of PFS in the company model were taken from the COMBI-d and COMBI-v trials and exclude all patients who progressed as per the trial definition but who remained on treatment. The utility values of people classified as being in the PFS state, therefore, do not reflect utility for all patients who are responding in some positive way to treatment.

Similarly, post-progression survival (PPS) utility values were captured for up to 125 patients in the COMBI-d trial, and for 183 in the COMBI-v trial, for patients who were responding positively to, and remained on, study treatment. The ERG, therefore, considers describing the PPS utility as 'post-progression' is inaccurate, especially as, in the company model, progression is the point at which study treatment stops.

The ERG considers that it would be more meaningful to apply utility values that are related to being 'on' or 'off' study treatment as determined by TTD data. This value was not collected directly during either the COMBI-d or COMBI-v trials. However, all of the patients in the PFS state were 'on treatment'. The ERG has used the average value over the first 16 weeks as the 'on treatment' utility value for all treatments. Sixteen weeks was chosen to allow sufficient time for any therapy related AEs and any response benefit from treatment to impact on utility measurement. The period of 16 weeks also reduces the bias that potentially exists from the removal of patients from the progression-free state who had progressed but who remained 'on treatment'. The ERG estimated this utility value to be [redacted]. This compares to the [redacted] utility value for PFS in the vemurafenib monotherapy STA.[11]

The ERG considers that, whilst not ideal, PPS utilities could be used to estimate an 'off treatment' utility value. In the COMBI-d trial, HRQoL data were collected up to 56 weeks for patients who were not considered to have progressed, at the point of progression and 5 weeks after progression. The ERG requested utility values for European patients in the COMBI-d trial at each point of collection.

For European patients in the trametinib+dabrafenib arm of the COMBI-d trial the utility value at the time of progression was [redacted], and at 5 weeks post-progression was [redacted] (Clarification response, QB3, Table 4.0105). A much smaller reduction was seen in the dabrafenib arm ([redacted] at the time of progression and [redacted] at 5 weeks). The ERG considers that, as the utility values for 'off treatment' are applied

up to a point 30 years from the commencement of study treatment, it would be more appropriate to pool the utility values 5 weeks post-progression from both arms of the COMBI-d trial rather than at the point of progression for the 'off treatment' utility, whilst recognising that some of the patients that generated this sample were actually still on treatment. The pooled estimated, from a total of 61 patients, is [redacted]. This is somewhat higher than the post progression utility used in the NICE appraisal of dabrafenib monotherapy[12] (0.59), although it is noted that in that model the value was not adjusted for age.

Age dependent utilities

The ERG considers that the utility values in the model should reflect declining utility with age. A utility decrement for age was therefore applied from the age of 60 to 75 years. The value was derived from Kind (1999)[70] who suggested that a one-off decrement of 0.02 should be applied at age 65 years and a further one-off decrement of 0.05 should be applied at age 75 years.

Utility value summary

A comparison of the utility values used by the company and the alternative values proposed by the ERG are shown in Table 35.

Table 35 Model utility values

State as described in CS	State as described by the ERG	Treatment	CS value*	ERG value**
PFS	"on treatment"	Trametinib+dabrafenib	0.837	[redacted]
		Dabrafenib	0.789	
		Vemurafenib	0.746	
PPS	"off treatment"	Trametinib+dabrafenib	0.697	[redacted]
		Dabrafenib		
		Vemurafenib		
	Age decrement	All	-	0.02 at 65 0.05 at 75

CS=company submission; ERG=Evidence Review Group: PFS=progression-free survival; PFS=post-progression survival
* Calculated based on the whole populations included in the d and COMBI-v trials
** Calculated by the ERG based on European patients included in the COMBI-d trial

The ERG applied their preferred utility estimates, both on and off treatment, to the company model. This resulted in discounted QALYs for patients treated with trametinib+dabrafenib, compared to the company base case, falling from 3.443 to [redacted]. For patients treated with dabrafenib the ERG changes reduced the QALYs gained from 2.146 to [redacted], and for patients treated with vemurafenib the QALYs increased from 2.098 to [redacted].

These changes increase the ICER for trametinib+dabrafenib compared to dabrafenib from £104,069 in the company base case to £114,084 per QALY gained and, compared to vemurafenib, from £96,436 to £111,146 per QALY gained.

5.5.6 Minor errors in the model

As well as the substantive changes that the ERG considers are required, there are a number of minor model errors that the ERG identified but has not altered due to the small impact they would have on the size of the ICERs.

Post progression monitoring costs

As well as PSACT costs, the company has applied a monthly monitoring cost of £389 once a patient has progressed. This includes an outpatient visit to an oncologist and monthly radiological examinations. This cost is applied every month until death. The ERG accepts that patients with melanoma may never be considered 'cured' or 'cancer free'. However, it also seems unreasonable to expect that 20 years or more after a patient has stopped taking a BRAF inhibitor therapy (when they are aged 75 years or more in the model) they would continue to receive monthly radiological examinations to check for progression. In total these (discounted) costs are £4,132 higher for trametinib+dabrafenib compared to dabrafenib or vemurafenib so are not insignificant.

The ERG considers that the impact of limiting these costs to, say, 5 years at least in a scenario analysis would have been informative. The current construction of the model makes this impossible to verify without significant redesign. However, the cost differential from limiting monitoring costs could not result in a reduction of total costs for trametinib+dabrafenib greater than the £4,132 differential that currently exists compared to dabrafenib and vemurafenib with on-going monitoring to death. If this £4,132 differential was removed, then the ICER for trametinib+dabrafenib compared to dabrafenib would decrease from £104,069 in the company base case to £100,945 per QALY gained and, compared to vemurafenib, would decrease from £96,436 to £93,365 per QALY gained. These ICERs show the maximum change that would be seen if a limit on monitoring time was introduced.

The increase in post progression life expectancy estimated by the company model is 4.0 years with trametinib+dabrafenib, 1.6 years longer than with dabrafenib and vemurafenib. This suggests that the majority of patients in all arms are dead by year 5 post-progression. Therefore, if a limit of 5 years were placed on monitoring costs then this would have limited impact on the post-progression monitoring costs

estimated by the model between arms. As such, given the minimal impact that the cost differential has on the size of the overall ICERs, the ERG considers that the assumption of on-going monitoring costs is acceptable and does not significantly influence the size of the estimates generated by the model.

Adverse event costs

The ERG considers that, from a cost perspective, the company model should have included more AEs than were actually included, notably those that occurred more often in patients treated with trametinib+dabrafenib rather than a BRAF inhibitor, such as diarrhoea.

However, the ERG considers that the cost of treating the common AEs would have been small relative to the costs of drug treatment included in the model. The model does not allow for easy addition of new AEs, so whilst not amending the model to include additional AEs, the ERG notes that as AEs that were more commonly associated with trametinib+dabrafenib treatment than with BRAF inhibitor monotherapy were not included in the model, the ICERs presented by the company and the ERG for trametinib+dabrafenib compared to BRAF inhibitor monotherapy may be slight underestimates.

Discounting

The company applied a discount rate at the end of every week after one year rather than annually as requested by NICE. The company model does not allow for the application of annual discounting without substantial reworking of the model. The ERG considers that the impact of using the NICE method on the size of the ICER, rather than that employed by the company, would be minimal.

AJCC case mix adjustment

The ERG notes that the company adjusted the AJCC registry data for the BRAF inhibitor arms using only the case mix from the COMBI-d trial rather than the case mix from both the COMBI-d and COMBI-v trials. As the ERG remodelled OS data using only data from the COMBI-d trial, this error does not affect the ERG results.

For completeness, a case mix adjustment using data from the COMBI-d and COMBI-v trials for the BRAF inhibitor monotherapy arm was calculated by the ERG and applied to the company base case model. This resulted in change of less than 2% to the size of the ICER for trametinib+dabrafenib compared to dabrafenib or vemurafenib.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Overview

The ERG has made the following changes to the company model to address the points raised in Section 5.5:

- Use of TTD data to estimate study treatment costs
- Use of equal PSACTs for the intervention and comparator therapies
- Application of on and off treatment utility values relating to European patients and adjusted for age
- Application of ERG method for estimating OS
- Use of COMBI-d trial data (instead of pooled data) and application of the ERG preferred method for estimating OS.

Cost effectiveness results for the comparison of treatment with trametinib+dabrafenib with dabrafenib are presented in Table 36 and those for the comparison of treatment with trametinib+dabrafenib with vemurafenib are presented in Table 37. Details of all of the Microsoft Excel revisions made by the ERG to the company model are presented in Appendix 3.

Table 36 Cost effectiveness results (trametinib+dabrafenib vs dabrafenib): ERG revisions to company base case comparison

Model scenario and revisions	Trametinib+dabrafenib			Dabrafenib			Incremental			ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs*	Life years	£/QALY
A. Company base case	**£[redacted]**	**3.443**	**4.586**	**£[redacted]**	**2.146**	***2.933***	**£135,058**	**1.297**	**1.653**	**£104,069**
R1) TTD data for on treatment costs	£320,153	3.443	4.586	£170,405	2.146	2.933	£149,748	1.297	1.653	£115,457
R2) Equal PSACT costs	£305,706	3.443	4.586	£156,754	2.146	2.933	£148,952	1.297	1.653	£114,843
R3) Application of on and off treatment utilities and age related decrement with European patient values	£[redacted]	[redacted]	4.586	£[redacted]	[redacted]	2.933	£135,418	1.187	1.653	£114,084
R4) Application of ERG OS amendments	£297,683	3.392	4.511	£165,262	2.514	3.461	£132,421	0.878	1.050	£150,821
R5) Use of COMBI-d trial data for OS with ERG amendments	£297,906	3.427	4.562	£166,286	2.677	3.696	£131,620	0.75	0.866	£175,493
B. Base case + (R1:R2)	**£327,794**	**3.443**	**4.586**	**£164,235**	**2.146**	**2.933**	**£163,559**	**1.297**	**1.653**	**£126,106**
C. Base case + (R1:R3)	**£327,794**	[redacted]	**4.586**	**£164,235**	[redacted]	**2.933**	**£163,559**	**1.187**	**1.653**	**£137,792**
D. Base case + (R1:R4)	**£327,467**	**3.255**	**4.511**	**£166,544**	**2.461**	**3.461**	**£160,923**	**0.794**	**1.050**	**£202,674**
E. Base case + (R1:R3, R5)	**£327,690**	**3.288**	**4.562**	**£167,568**	**2.616**	**3.696**	**£160,122**	**0.672**	**0.866**	**£238,277**

*CS QALYs=1.298, ERG correction=1.297
ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PSACT=post-study anti-cancer therapy; TTD=time to treatment discontinuation; QALYs=quality adjusted life years

Table 37 Cost effectiveness results (trametinib+dabrafenib vs vemurafenib): ERG revisions to company base case comparison

Model scenario and revisions	Trametinib+dabrafenib			Vemurafenib			Incremental			ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY
A. Company base case	**£[redacted]**	**3.443**	**4.586**	**£[redacted]**	**2.098**	***2.933***	**£129,707**	**1.345**	**1.653**	**£96,436**
R1) TTD data for on treatment costs	£320,153	3.443	4.586	£176,803	2.098	2.933	£143,350	1.345	1.653	£106,580
R2) Equal PSACT costs	£305,706	3.443	4.586	£166,319	2.098	2.933	£139,387	1.345	1.653	£103,633
R3) Application of on and off treatment utilities and age related decrement with European patient values	£[redacted]	[redacted]	4.586	£[redacted]	[redacted]	2.933	£129,707	1.167	1.653	£111,146
R4) Application of ERG OS amendments	£297,683	3.392	4.511	£170,613	2.467	3.461	£127,070	0.925	1.050	£137,373
R5) Use of COMBI-d trial data for OS with ERG amendments	£297,906	3.427	4.562	£171,637	2.630	3.696	£126,269	0.797	0.866	£158,430
B. Base case + (R1:R2)	**£327,794**	**3.443**	**4.586**	**£175,127**	**2.098**	**2.933**	**£152,667**	**1.345**	**1.653**	**£113,507**
C. Base case + (R1:R3)	**£327,794**	[redacted]	**4.586**	**£175,127**	[redacted]	**2.933**	**£152,667**	**1.167**	**1.653**	**£130,820**
D. Base case + (R1:R4)	**£327,467**	**3.255**	**4.511**	**£177,436**	**2.461**	**3.461**	**£150,031**	**0.794**	**1.050**	**£188,956**
E. Base case + (R1:R3, R5)	**£327,690**	**3.288**	**4.562**	**£178,460**	**2.616**	**3.696**	**£149,230**	**0.672**	**0.866**	**£222,068**

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PSACT=post-study anti-cancer therapy; TTD=time to treatment discontinuation; QALYs=quality adjusted life years

6.2 ERG conclusions of cost effectiveness evidence

The ERG considers that there are several fundamental issues that cast doubt on the cost effectiveness results produced by the company model.

First, the company model has a basic flaw in its design whereby the less effective trametinib+dabrafenib treatment is at maintaining patients in a progression-free state relative to comparators, the more cost effective it becomes. Not only is this counterintuitive, it also makes any exploration of the assumptions made around PFS spurious and misleading and casts doubt on the robustness of the model and its findings. Both the company and ERG ICERs should therefore be interpreted with caution.

Second, the company has substantially underestimated the survival of patients on BRAF inhibitor monotherapy and has therefore substantially underestimated the ICER for trametinib+dabrafenib compared to BRAF inhibitor monotherapy. The ERG also considers that a more accurate estimate of survival is generated by looking at the unblinded, placebo controlled data from the COMBI-d trial only rather than the company approach of pooling survival data from the COMBI-d trial with data from the open-label COMBI-v trial.

Third, the ERG considers that, as approximately one third of patients in the COMBI-d and COMBI-v trials received treatment post-progression for a mean duration of between 3 and 6 months, PFS is an unreasonable estimate of time on treatment even after an adjustment for RDI is made. The ERG considers that use of TTD data is more appropriate for the measurement of treatment costs as well as for the measurement of utility whilst on treatment. The ERG considers that the application of PSACT costs should be equal across all arms and that there is no statistical or clinical justification for the application of differential utility values for patients receiving different treatments.

Fourth, the ERG applied utility values in the company model based on whether patients were on or off treatment rather than by progression status. The ERG found no robust statistical evidence that differential utilities should be applied based upon treatment arm and so the same on and off treatment utilities were applied regardless of whether patients received trametinib+dabrafenib or BRAF inhibitor monotherapy.

The ERG considers that the use of time on treatment and utility data from the open-label COMBI-v trial introduces unnecessary bias into the model when blinded data from the COMBI-d trial are available. The ERG therefore excluded data from the COMBI-v trial from the amended analyses of these variables.

Application of the ERG changes to OS, costs and utility using pooled data from the COMBI-d and COMBI-v trials for OS resulted in an ICER for trametinib+dabrafenib compared to dabrafenib of £202,674 per QALY gained and for trametinib+dabrafenib compared to vemurafenib of £188,956 per QALY gained. If only data from the COMBI-d trial for OS are used then the ICER for trametinib+dabrafenib compared to dabrafenib is £238,277 per QALY gained and that for trametinib+dabrafenib compared to vemurafenib is £222,068 per QALY gained.

7 END OF LIFE

The company puts forward the case (CS, Section 4.13.3) that trametinib+dabrafenib meets the NICE End of Life criteria.[64]

The NICE criteria for applying a less restrictive assessment of cost effectiveness for End of Life are that:

- treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment and
- treatment is licensed, or otherwise indicated, for small patient populations.

The company claims that trametinib+dabrafenib meets the NICE End of Life criteria for the reasons set out in Table 38.

Table 38 Company End of Life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS data from BRAF inhibitor monotherapy arms of RCTs: **Dabrafenib** BREAK-3=20.1 months COMBI-d=18.7 months **Vemurafenib** BRIM-3=13.6 months COMBI-v=18 months
The treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment	**COMBI-d** Median OS gain trametinib+dabrafenib vs dabrafenib+placebo = 6.4 months **COMBI-v** Median OS gain trametinib+dabrafenib vs vemurafenib= 7.6 months
The treatment is licensed or otherwise indicated, for small patient populations	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

OS=overall survival
Source: CS, p176

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

The ERG agrees with the company that treatment with trametinib+dabrafenib offers a mean extension to life of at least 3 months when compared with dabrafenib or vemurafenib monotherapy. The ERG notes that a comparison of the life-extension benefit of trametinib+dabrafenib compared with either ipilimumab or pembrolizumab is not available.

The ERG also agrees with the company that trametinib+dabrafenib is licensed for a small patient population.

8 DISCUSSION

The company presented evidence from two RCTs, the COMBI-d trial (trametinib+dabrafenib versus dabrafenib+placebo) and the COMBI-v trial (trametinib+dabrafenib versus vemurafenib). Results from the COMBI-d trial demonstrate that compared to treatment with dabrafenib, trametinib+dabrafenib statistically significantly improves OS, PFS and ORR. Results from the COMBI-v trial also demonstrate that compared to treatment with vemurafenib, trametinib+dabrafenib statistically significantly improves OS, PFS and ORR. The ERG agrees with the company that trametinib+dabrafenib appears to be clinically effective when compared with dabrafenib+placebo and when compared with vemurafenib.

8.1 Current treatment pathway

Over the last 6 years five new treatments have been recommended by NICE[10-16] for patients with advanced (unresectable or metastatic) melanoma, namely two BRAF inhibitors (vemurafenib and dabrafenib) and three immunotherapies (ipilimumab, pembrolizumab and nivolumab). However, the speed at which new treatment options have become available has not been matched by the availability of clinical evidence demonstrating the optimal sequencing of these treatments

For patients with rapidly progressing, high volume, disease or those whose metastatic disease has caused them to be unwell, a BRAF inhibitor remains the first-line treatment of choice as there is a high probability that it will induce a fast response. However, disease progression after a number of months is inevitable and only a proportion of these patients may be fit enough to receive a second-line therapy. For fitter patients with lower volume disease, those who have more indolent disease, and those who have minimal symptoms from their metastatic disease, the choice is whether to offer immunotherapy or BRAF inhibitor monotherapy as the first-line of treatment. The rationale for prioritising immunotherapy over a BRAF inhibitor is to reserve the BRAF inhibitor monotherapy as a salvage therapy in the event of symptomatic progression.

Long-term data on treatment efficacy are limited. Furthermore, the clinical situation is likely to become more complex as trials investigating the efficacy of several combination treatments are expected to report in the coming years. However, based on the relatively short-term evidence from the COMBI-d and COMBI-v trials, clinicians are likely to be in favour of treating patients with the combination of trametinib+dabrafenib rather than with a BRAF monotherapy. Compared with BRAF inhibitor monotherapy, treatment with trametinib+dabrafenib results in improved PFS and OS outcomes and is associated with fewer new skin cancers.

8.2 Relevance of PFS as an endpoint

The RECIST criteria, which were employed in both the COMBI-d and COMBI-v trials to assess disease progression, were originally developed to measure the efficacy of chemotherapy treatments. The RECIST criteria are relevant to BRAF inhibitor treatment as BRAF inhibitors target cell proliferation and thereby shrink tumours. However, RECIST criteria are less relevant when assessing the efficacy of treatments that trigger an immune response. An immune response can result in inflammation which can look like disease progression. Immune-related response criteria (irRC) are increasingly being used in RCTs as they offer a more comprehensive evaluation of immunotherapies than the RECIST criteria.[71]

The protocols for both the COMBI-d and COMBI-v trials permitted continuation of study treatment post-progression. Around 30% of patients in both arms of both trials continued to receive study treatment after disease progression, with the mean time on treatment post-progression ranging from over 70 days in the vemurafenib arm of the COMBI-v trial to over 200 days in the trametinib+dabrafenib arm of the COMBI-d trial. The ERG suggests that if continuing on BRAF inhibitor therapy after confirmed disease progression (using traditional criteria) is common practice in RCTs and in the NHS, then it would be helpful to record, and report, both PFS and TTD outcomes.

8.3 End of Life

The first criterion[64] that must be met for a treatment to be considered as an End of Life treatment by NICE is that “The treatment is indicated for patients with a short life expectancy, normally less than 24 months”. The assessment of whether a treatment meets this criterion is generally based on the magnitude of median OS. However, this submission highlights that mean OS should also be considered.

In the case of malignant melanoma, the OS survival distribution is heavily skewed, with approximately 50% of patients being dead within 2 years (as evidenced by the COMBI-d and COMBI-v trial results) and a long tail of patients living for a substantial amount of time. Indeed, the AJCC registry data[4] show that approximately 10% of patients are still alive at 10 years. The ERG notes that this figure may be conservative as it is based on data collected during a period prior to the availability of either BRAF inhibitors or immunotherapy as treatments for this patient population. Furthermore, the ERG model suggests that the mean life expectancy for the whole population is close to 4 years – twice the expectancy required for a technology to be considered under NICE’s End of Life criteria.

This disparity between median and mean OS leads to a consideration of equity. A disease could have a survival distribution such that there is a steady mortality rate up to 25 months, at which point 50% of patients are dead, and then the mortality rate increases such that all patients are dead by the end of 3 years. In such a situation median OS would be more than 2 years, whilst mean OS would be less than 2 years. Patients with such a disease could be considered as having a short life expectancy but treatment for the disease would not meet the NICE short life expectancy criterion.

The ERG considers that assessment of short life expectancy should take into account median survival, mean survival and the length of the tail of the survival distribution. Such an approach would lead to a more equitable assessment of whether a treatment should be considered under NICE's End of Life criteria.

8.4 Health-related quality of life

The ERG welcomes the fact that the EQ-5D questionnaire was employed in the COMBI-d and the COMBI-v trials, meaning that HRQOL data have been collected from patients rather than, as is often the case, from clinicians or members of the general public. However, the ERG has some concerns about the extent to which the collected data may be considered representative of the experience of the whole melanoma population. For example, the ERG has observed that in the trametinib+dabrafenib arms of the COMBI-d and COMBI-v trials the utility scores at week 40 and week 48 are higher than those at baseline (+0.01 and +0.07). Similarly, data from both the COMBI-d and the COMBI-v trials show that the utility scores at the point of disease progression for patients receiving trametinib+dabrafenib are higher than those at baseline (+0.04 and +0.06 respectively). These observations may reflect the fact that only patients who feel well completed the questionnaires.

8.5 Pooling of blinded, placebo controlled trials with open label trials

This evidence presented in the CS essentially comes from two trials which were all but identical except that one was fully blinded and placebo controlled and the other was an open-label trial i.e. no blinding and no placebo. The evidence from the trials, therefore, presents an opportunity to explore how blinding and placebo control can influence results and minimise bias.

The differences in key outcomes such as TTD, utility and OS have been discussed at length in the main body of this report. In addition, there are several key messages for future company submissions that can be taken from these discussions:

- There is no statistical test that can confirm that data from a trial with less than optimal study design does not suffer from bias
- Pooling OS K-M data from trials with apparently similar OS, based on a comparison of point statistics between the trials, can result in substantially different ICERs per QALY gained compared to the ICERs per QALY gained that are generated without pooling
- Where robust data from gold standard RCTs are available, these data should be presented separately from any analysis that pools gold standard data with data from trials that are of a lower methodological quality.
- If utility data from open-label studies are used when data are available from studies with a higher quality design then the use of data from the open-label studies must be justified.

8.6 Three state cancer models (PFS, PPS and death)

The model structure used by the company is one that has been used in previous appraisals of cancer therapies, most recently in the appraisal of pembrolizumab for treating ipilimumab naïve unresectable, metastatic melanoma.[15] If this structure is to be used in future submissions, then, to ensure that the model is internally consistent, differential morality hazards needs to be linked to the PFS and PPS states. The issue of using differential mortality hazards is particularly important in models where treatment cost is linked to the PFS state. Failure to implement differential mortality hazards leads to a model with little face validity which produces erroneous results. Furthermore, scenario analyses around clinical effectiveness are rendered meaningless.

9 OVERALL CONCLUSIONS

9.1 Implications for research

A key issue for clinicians is whether to use a BRAF inhibitor or immunotherapy for the initial treatment of patients with advanced (unresectable or metastatic) BRAF positive-melanoma. Further research examining the optimal treatment pathway for the use of BRAF inhibitors, ipilimumab, pembrolizumab and nivolumab is urgently needed.

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11 APPENDICES

11.1 Appendix 1: Description and critique of the company's search strategies

Clinical effectiveness

Searches were reported for the databases; Medline (via embase.com), Embase, Medline in process (via PubMed) and CENTRAL (via the Cochrane Library). The searches were run from inception to 13 July 2015. The searched included the use of an RCT filter, melanoma search terms, drug terms and drug comparator terms. The company reported hand searches undertaken (2012 to October 2015) to identify additional studies in the American Society of Clinical Oncology, the European Society for Medical Oncology and the Society of Melanoma Research, the European Cancer Organisation and the International Society for Pharmacoeconomics and Outcomes Research. In addition the company searched the European Medicines Agency, Food and Drug Administration, Health Technology Assessment, National Institute of Health and Care Excellence, Scottish Medicines Consortium and other HTA organisations for additional public assessment reports. It does not appear that the company carried out searches for non RCT information.

The full search strategies included in the appendices indicate the search terms included were relevant and included MeSH and free text and an RCT filter.

Cost effectiveness

The company searched the same databases for the cost effectiveness searches as the clinical effectiveness searches but included NHS EED. The same hand searches were also undertaken. The company states (CS, section 5.4.3) that a comprehensive review was carried out for health related quality of life studies; however, no databases or date information has been provided for these searches.

The company carried out searches for identification, measurement and valuation and quality of life. Both searches are documented in Appendix 8.11 of the CS and the company used appropriate search filters and melanoma terms for the search.

11.2 Appendix 2: Supporting evidence from the BRF113220 (Part C) trial

The company provides supporting evidence for the clinical effectiveness of trametinib+dabrafenib versus dabrafenib monotherapy from a Phase II randomised, open-label, multicentre, dose-ranging trial. The BRF113220 (Part C) trial[72,73] recruited 162 patients with BRAF V600 mutation-positive metastatic melanoma who could have received one chemotherapy treatment in the advanced or metastatic setting. The trial was conducted in the US and Australia. Patients were randomised to one of three treatment arms: dabrafenib monotherapy, trametinib (1mg) combined with dabrafenib or trametinib (2mg) combined with dabrafenib. The co-primary endpoints of the trial were PFS, ORR an duration of response.

The key baseline characteristics of the recruited patients are shown in Table 39. The ERG notes an imbalance in the mean ages of patients between the treatment arms (51.8, 49.9 and 55.9 years respectively), an imbalance in the percentages of patients at stage M1b and an imbalance in numbers of patients treated with prior chemotherapy.

Table 39 Key characteristics of patients recruited to the BRF113220 (Part C) trial

	BRF113220 (Part C) treatment arms			
	Dabrafenib monotherapy N=54	**Trametinib (1mg) + dabrafenib N=54**	**Trametinib (2mg) + dabrafenib N=54**	**Total N=162**
Age (years)				
Mean (SD)	51.8 (15.19)	49.9 (14.70)	55.9 (11.85)	52.5 (14.13)
Sex, n (%)				
Male	29 (54)	30 (56)	34 (63)	93 (57)
ECOG PS 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)
Stage, n (%)				
IIIC	1 (2)	1 (2)	0	2 (1)
IV	53 (98)	53 (98)	54 (100)	160 (99)
M Stage 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)
LDH n (%)				
≤ ULN	27 (50)	29 (54)	32 (59)	88 (54)
≥ ULN	27 (50)	25 (46)	22 (41)	74 (46)
Number disease sites, n (%)				
≥3	34 (63)	27 (50)	28 (52)	89 (55)
≤3	20 (37)	27 (50)	26 (48)	73 (45)
Prior chemotherapy or interleukin 2, n (%)				
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)
Brain metastases (prior history) n (%)				
No	50 (93)	47 (87)	52 (96)	149 (92)
Yes	4 (7)	7 (13)	2 (4)	13 (8)

a 2 patients were classified as stage IIIc M0
* 6 patients received prior anti-cancer regimens that could not be easily classified as advanced or metastatic regimens
ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; SD=standard deviation; ULN=upper limit of normal

11.2.1 Risk of bias assessment for the BRF113220 (Part C) trial

The company conducted a risk of bias assessment based on the criteria recommended by the Centre for Reviews and Dissemination at the University of York.[41] The results of the company's assessment along with the ERG comments are presented in Table 40.

Table 40 Company's risk of bias assessment for the BRF113220 (Part C) trial

Risk of bias criteria	BRF113220 (Part C)	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	No. Treatment allocation was not concealed as this was an open-label study	Disagree. Patients were randomised via IVRS and therefore treatment allocation was concealed
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Agree
Were there any unexpected imbalances in drop-outs between groups?	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree
Did the analysis include an intention-to-treat analysis? Was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree

11.2.2 Results of the BRF113220 (Part C) trial

The company appropriately reports only the outcomes of patients who were treated with the licensed dose of trametinib (2mg) in combination with dabrafenib versus dabrafenib monotherapy. The outcomes of the trial are presented in Table 41. All outcome data reported are based in 12 months of follow-up.

Investigator-assessed progression-free survival

Median PFS (investigator-assessed) was 9.4 months in the trametinib+dabrafenib arm compared with 5.8 months in the dabrafenib monotherapy arm, a difference of 3.6 months. The reduction in risk associated with trametinib+dabrafenib was 61% (HR=0.39; 95% CI: 0.25 to 0.62, p<0.0001). The K-M curves (CS, Figure 17) show an early separation that is sustained across follow-up.

The results of a further, post-hoc analysis of PFS based on data at a median follow-up of 34 months is reported in the CS (CS, p121). Median PFS in the trametinib+dabrafenib arm was 9.4 months, compared with 5.8 months in the dabrafenib monotherapy arm, a difference of 3.6 months (HR=0.41; 95% CI:0.27 to 0.64).

The company conducted a BIRC of PFS at 12 months. The results of the blinded review yielded a risk reduction of 0.45% for trametinib+dabrafenib (HR=0.55; 95% CI: 0.33 to 0.93), lower than the 61% calculated for the investigator-assessed review. The company (CS,

p121) considers that the difference is due to informative censoring in that new lesions identified at the investigation site were not considered at the central review to be conclusive signs of evidence of progression.

Overall response rate and duration of response

The ORR in the trametinib+dabrafenib arm (76%) was greater than that recorded in the dabrafenib monotherapy arm (54%). The 22% difference was statistically significant, p=0.0264. The duration of response was also longer in the trametinib+dabrafenib arm compared with the dabrafenib monotherapy arm (10.5 months versus 5.6 months).

Overall survival

The company reports that at 12 months follow-up, median OS had not been reached. The company also states (CS, p122) that 80% of patients initially randomised to the dabrafenib monotherapy arm had switched to receiving treatment with trametinib+dabrafenib.

The company has conducted several updated OS analyses updates CS, Table 46). The most recent update, based on 46 months of follow up, demonstrated that median OS in the trametinib+dabrafenib arm was 25 months compared with 20.2 months in the dabrafenib monotherapy arm (HR=0.77; 95% CI:0.49 to 1.21). The company states that the 83% crossover rate from dabrafenib monotherapy to trametinib+dabrafenib has impacted on the OS results and the company presents OS results (at 46 months of follow-up) that are adjusted for treatment crossover using the RPFSTM method (HR=0.55; 95% CI0.20 to 1.55).

The company concludes (CS, p125) that compared with dabrafenib monotherapy, treatment with trametinib+dabrafenib is associated with a clinically relevant reduction in the risk of death.

Table 41 Key results for the BRF113220 (Part C) trial

	Trametinib (2mg) + dabrafenib N=52	Dabrafenib monotherapy N=54
Investigator-assessed PFS – Co-primary outcome		
Patient 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)
Estimates for PFS (months)[a]		
1st quartile (95% CI)	5.8 (5.3 to 8.7)	3.8 (3.6 to 5.5)
Median (95% CI)	9.4 (8.6 to 16.7)	5.8 (4.6 to 7.4)
3rd quartile (95% CI)	16.7 (12.4 to 16.7)	9.1 (7.4 to 9.4)
HR Estimate [b] (95% CI)	0.39 (0.25 to 0.62)	
Stratified log rank p-value[c]	<0.0001	
ORR – Co-primary outcome		
CR+PR, n (%) 95% CI	41 (76) (62.4 to 86.5)	29 (54) (39.6 to 67.4)
p-value[a]	0.0264	
Duration of response Median, months (95% CI)[d]	10.5 (7.4 to 14.9)	5.6 (4.5 to 7.4)
OS		
Patient classification n (%)		
Died (event)	14 (26)	19 (35)
Censored, follow-up ended	0	0
Censored, follow-up ongoing	40 (74)	35 (65)
Estimates for OS (months)[a]		
1st quartile (95% CI)	12.7 (9.6 to NR)	10.7 (7.9 to 13.4)
Median (95% CI)	NR (NR to NR)	NR (13.4 to NR)
3rd quartile (95% CI)	NR (NR to NR)	NR (NR to NR)
Adjusted HR Estimate [b] (95% CI)	0.67 (0.34 to 1.34)	
Stratified log rank p-value[b]	0.2591	
Estimates for OS at 1 year (%)		
1 year (95% CI)	79 (66 to 88)	70 (55 to 80)

a. Confidence intervals were estimated using the Brookmeyer Crowley method.
b. Hazard ratio estimated using Pike estimator. A hazard ratio <1 indicates a lower risk with combination compared with monotherapy.
c. P-values are based on 2-sided log rank test. The censoring method included censoring for extended loss to follow-up, new anti-cancer therapy, and excluding symptomatic progression.
d . p-values and 95% CIs were calculated based on the unconditional exact method
HR=hazard ratio; NR=not reached
Source: CS, adapted from Table 43, Table 44, Table 45

11.2.3 Health-related quality of life

No HRQoL data were collected as part of the BRF113220 study.

11.2.4 Subgroup analyses

The company conducted a series of subgroup analyses of data from the BRF1132220 (Part C) trial. The analyses listed were:

- 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).

The company reports (CS, p131) that for PFS, the results of all subgroups analyses were consistent with the ITT analysis (CS, Figure 23). For ORR, treatment with trametinib+dabrafenib was more effective than dabrafenib monotherapy, with the exception of patients with stage IIIc, IV M0, IVM1a or stage IVM1b disease; no difference in efficacy was recorded for these subgroups.

The ERG notes that there were small numbers of patients in each arm of the BRF1132220 (Part C) trial (n=52 and n=54). It is therefore difficult to draw any firm conclusions from the results of subgroup analyses.

Adverse events in the BRF113220 (Part C) trial

Detailed information relating to the adverse events experienced by patients in the BRF113220 (Part C) trial is presented in the CS (CS, ps 153 to 159).

The company reports (CS, p154) that there were greater incidences of AEs in the trametinib+dabrafenib arm compared to the dabrafenib monotherapy arm that resulted in the following events:

- dose reductions (60% versus 25%)
- interruptions to treatment (73% versus 34%)
- discontinuation of treatment (15% versus 2%)
- serious AEs (69% versus 26%)
- drug-related AEs (45% versus 19%)
- fatal AEs (7% versus 0%).

The most common AEs (CS, p138) (≥20% frequency) associated with treatment with trametinib+dabrafenib were pyrexia ((69% versus 26%), chills (60% versus 17%), fatigue (58% versus 42%), nausea (47% 21%), vomiting (47% versus 15%) and diarrhoea (49% 28%). The company concludes that these AEs are consistent with those recorded in the COMBI-d and COMBI-v trials.

Of the grade 3 and grade 4 AEs (≥2% of patients), 58% were reported in the trametinib+dabrafenib arm compared with 42% in the dabrafenib arm (CS, p155). The most common AEs of grade 3 or grade 4 in the trametinib+dabrafenib arm were neutropenia (2%) and hyponatraemia (2%). The most common AEs of grade 3 or grade 4 in the dabrafenib arm were squamous cell carcinoma of the skin (9%), squamous cell carcinoma (8%) and fatigue (6%).

Serious AEs (≥2% of patients) were more frequent in the trametinib+dabrafenib arm compared with the dabrafenib arm (62% versus 25%). The most frequently reported SAE in the trametinib+dabrafenib arm were pyrexia (25%) and chills (18%). The most frequently reported SAE in the dabrafenib arm was squamous cell carcinoma (6%).

11.3 Appendix 3: ERG revisions to the company model

This appendix contains details of the changes that the ERG made to the company model. Information contained within the file named ERG_T+D.xlsx is needed to replicate the ERG's cost effectiveness results.

ERG revisions (Table 36 and Table 37)	**Implementation instructions**
R1. TTD data for on treatment costs	Paste worksheet '**TTD**' from ERG_T+D.xlsx into company model *For vemurafenib and dabrafenib* In Sheet 'SurvCalc' Insert formula in cell **N28**=VLOOKUP(D33,TTD!$A$3:$C$302,2) Copy cell **N28** to **N29:L1071** *For trametinib+dabrafenib* In Sheet 'SurvCalc' Insert formula in cell **N28**=VLOOKUP(D33,TTD!$A$3:$C$302,3) Copy cell **N28** to **N29:L1071**
R2 Equal PSACT costs	In Sheets 'Maininputs' Set value in cell C29 = £63280 Set value in cell H29 = £63280 Set value in cell M29 = £63280

R3 Application of on and off treatment utilities and age related decrement with European patient values This amendment will adjust both costs and utilities. The utility changes are used in the scenario but the costs for the scenario are taken from the base case results.	Paste worksheet '**TTD**' from ERG_T+D.xlsx into company model <u>In Sheets 'LifeTableCalc'</u> Insert formula in cell **B39**= $B37*(1-$B$8-$B$9-0.05) <u>In Sheets 'CostQALYCalc'</u> Insert formula in cell **B81**= (SUMPRODUCT($M$7:$M$528,$H$7:$H$528,$I$7:$I$528)*(1-$B$26))*7/365+(SUMPRODUCT($M$529:$M$1050,$H$529:$H$1050,$I$529:$I$1050)*(1-$B$26-0.05))*7/365+((SUMPRODUCT($N$7:$N$528,$H$7:$H$528,$I$7:$I$528))*(1-$B$26-$B$27)+(SUMPRODUCT($N$529:$N$1050,$H$529:$H$1050,$I$529:$I$1050))*(1-$B$26-$B$27-0.02))*7/365-(AECalc!$B$16*$B$25)+LifeTableCalc!$B$39 <u>In Sheet 'Maininputs'</u> Set value in cell C41=0.194 Set value in cell H41=0.194 Set value in cell M41=0.194 Set value in cell C41=0.136 Set value in cell H41=0.136 Set value in cell M41=0.136 <u>*For vemurafenib and dabrafenib:*</u> <u>In Sheet 'SurvCalc'</u> Insert formula in cell **N28**=VLOOKUP(D33,TTD!$A$3:$C$302,2) Copy cell **N28** to **N29:L1071** <u>*For trametinib+dabrafenib*</u> <u>In Sheet 'SurvCalc'</u> Insert formula in cell **N28**=VLOOKUP(D33,TTD!$A$3:$C$302,3) Copy cell **N28** to **N29:L1071**

R4. Application of ERG OS amendments	In Sheet 'OS Profiles' Set value in cell G6=27 Set value in cell G8=27 Set value in cell I6=27 Set value in cell I8=27 Set value in cell J6=27 Set value in cell J8=27 In Sheet 'Parametric Survival Inputs Set value in cell G5=27 Set value in cell G6=27
R5. Use of COMBI-d date for OS with ERG amendments	Paste Worksheet **'K-M OS COMBI-d'** from ERG_T+D.xlsx into the company model In Sheet 'K-M OS COMBI-d' Copy cells A3:B1046 In sheet 'Empirical Survival Inputs' Paste in cells C5:D1048 In Sheet 'K-M OS COMBI-d' Copy cells C3:D1046 In sheet 'Empirical Survival Inputs' Paste in cells G5:H1048 In Sheet 'OS Profiles' Set value in cell G6=27 Set value in cell G8=27 Set value in cell I6=27

	Set value in cell I8=27 Set value in cell J6=27 Set value in cell J8=27 <u>In Sheet 'Parametric Survival Inputs</u> Set value in cell G5=27 Set value in cell G6=27