

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Trametinib in combination with dabrafenib for
treating unresectable or metastatic melanoma**

1 Recommendations

- 1.1 Trametinib in combination with dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic melanoma in adults with a BRAF V600 mutation only when the company provides trametinib and dabrafenib with the discounts agreed in the patient access schemes.

2 The technology

- 2.1 Trametinib (Mekinist, Novartis Pharmaceuticals) is an inhibitor of MEK1 and MEK2 kinases. Trametinib inhibits the action of the abnormal BRAF protein, with the aim of slowing the growth and spread of the cancer. Dabrafenib (Tafinlar, Novartis Pharmaceuticals) is a selective inhibitor of BRAF V600 kinase activity. It aims to block the activity of mutant protein kinase causing the cancer cells to stop growing and die. Trametinib and dabrafenib have marketing authorisations in the UK, as monotherapies and in combination with each other, for treating adults with unresectable or metastatic melanoma with a BRAF V600 mutation. Both trametinib and dabrafenib are taken orally.
- 2.2 The most common adverse reactions with trametinib in combination with dabrafenib are pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, and vomiting. For full details of adverse reactions and contraindications, see the summary of product characteristics.

- 2.3 The acquisition cost of trametinib is £1,120 per pack of 2-mg tablets (7 tablets per pack) (excluding VAT; Monthly index of medical specialties) and the cost of dabrafenib is £1,400 per pack of 75-mg tablets (28 tablets per pack) (excluding VAT; 'British national formulary' [BNF] edition 67). The company has agreed patient access schemes with the Department of Health. These schemes provide simple discounts to the list prices of trametinib and dabrafenib with the discounts applied at the point of purchase or invoice. The levels of the discounts are commercial in confidence. The Department of Health considered that these patient access schemes do not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 8) considered evidence submitted by Novartis Pharmaceuticals and a review of this submission by the evidence review group (ERG; section 9). See the [committee papers](#) for full details of the evidence.

Clinical effectiveness

- 3.1 The company identified 2 phase III randomised controlled trials (COMBI-d and COMBI-v) that assessed the clinical effectiveness of trametinib plus dabrafenib in people with histologically-confirmed stage IIIC (unresectable) or stage IV (metastatic) BRAF V600E/K mutation-positive melanoma. The trials included people who had an Eastern Co-operative Oncology Group (ECOG) performance statue of 0 or 1, with unresectable or metastatic melanoma that had not been treated before. Fewer than 20 patients had brain metastases.
- 3.2 COMBI-d was a double-blind, multicentre randomised controlled trial that compared trametinib (2 mg once daily) plus dabrafenib (150 mg twice daily; n=211) with dabrafenib monotherapy (150 mg twice daily with placebo control; n=212). COMBI-v was an open label, multicentre randomised controlled trial that compared trametinib (2 mg once daily)

plus dabrafenib (150 mg twice daily; n=352) with vemurafenib monotherapy (960 mg twice daily; n=352).

- 3.3 The company stated that the demographic disease characteristics and prognostic factors in both trials were generally well balanced between the treatment groups at baseline. In COMBI-v, after the pre-planned cut off, the Independent Data Monitoring Committee recommended stopping the study early due to superior efficacy in the trametinib plus dabrafenib group. As a result the study protocol for COMBI-v was amended to allow crossover from vemurafenib to the trametinib plus dabrafenib group. Crossover was not permitted in COMBI-d.
- 3.4 The company reported statistically significant and clinically meaningful differences in overall survival (OS) between the trametinib and dabrafenib combination group and the monotherapy groups at the final cut-off point in both trials. In COMBI-d there as a median OS of 25.1 months in the trametinib plus dabrafenib group compared with 18.7 months in the dabrafenib monotherapy group, with a corresponding hazard ratio (HR) of 0.71 (95% confidence interval [CI] 0.55 to 0.92). In COMBI-v there was a median OS of 25.6 months in the trametinib plus dabrafenib group compared with 18.0 months in the vemurafenib monotherapy group, with a corresponding hazard ratio of 0.66 (95% CI 0.53 to 0.81).
- 3.5 The progression-free survival (PFS) results based on investigator assessment from COMBI-d showed, at final cut off, a median PFS of 11.0 months in the trametinib plus dabrafenib group compared to 8.8 months in the dabrafenib monotherapy group (HR=0.67; 95% CI 0.53 to 0.84). Results from COMBI-v showed a median PFS of 12.6 months in the combination group compared with 7.3 months for vemurafenib alone (HR=0.61; 95% CI 0.51 to 0.73).
- 3.6 The company presented health-related quality of life results from both trials using 2 measures; the EuroQol-5 dimension questionnaire (EQ-5D) and the European Organisation for Research and Treatment of Cancer

Quality of Life Questionnaire-Core 30 (EORTC-QLQ-30). The rates of completion of EORTC-QLQ-30 among patients in both studies, and of EQ-5D in COMBI-v (the company did not present EQ-5D completion rates for COMBI-d), were over 90% at baseline, and over 70% at disease progression. For COMBI-d, EQ-5D scores at baseline were similar between treatment groups with a statistically significant difference in results favouring the combination group at week 16 only. Results from COMBI-v showed similar baseline EQ-5D scores between treatment groups and, for all assessments, the differences between scores were significantly better for the combination group compared with the monotherapy group. EORTC-QLQ-30 global health scores in COMBI-d were significantly better at weeks 8, 16 and 24 for trametinib plus dabrafenib compared with dabrafenib alone but not at other time points. The company reported that the EORTC-QLQ-30 global health scores in COMBI-v were significantly better for patients in the trametinib plus dabrafenib group compared with vemurafenib alone.

- 3.7 Approximately half of the adverse events experienced by patients having trametinib plus dabrafenib were mild-to-moderate in severity (grade 1 and grade 2). In both studies, the rates of grade 3 and grade 4 adverse events were higher in the monotherapy groups than in the combination groups (50% and 45% in COMBI-d; 57% and 66% in COMBI-v). In both studies, pyrexia and hypertension were the most common grade 3–4 adverse events in the trametinib plus dabrafenib group. Fewer skin-related toxicities were reported in the combination group. Adverse events leading to treatment discontinuation, dose reductions or dose interruptions were more common in the trametinib plus dabrafenib group compared with dabrafenib alone in COMBI-d, but in COMBI-v the proportions were generally similar between the trametinib plus dabrafenib group and the vemurafenib monotherapy group.

Evidence review group comments

- 3.8 The evidence review group (ERG) considered COMBI-d to be well designed and to have a low risk of bias. It reported that COMBI-v was of good quality but that the trial was open-label and did not include a placebo control or a blinded independent review of the secondary outcomes, which could lead to bias. The ERG commented that, in both trials, patients had not had treatment before and that there is no evidence for the use of trametinib plus dabrafenib as a second line treatment following immunotherapy.
- 3.9 The ERG agreed with the company that trametinib plus dabrafenib demonstrated greater clinical effectiveness compared with dabrafenib or vemurafenib alone. The ERG commented on the representativeness of the EQ-5D data collected in the trials. It noted that in the trametinib plus dabrafenib groups of COMBI-d and COMBI-v the utility scores at week 40 and week 48 were higher than those at baseline (+0.01 and +0.07 respectively). Similarly, data from both trials showed that the utility scores at the point of disease progression for patients having the combination treatment were higher than those at baseline (+0.04 and +0.06 respectively). The ERG considered that these observations may be because only patients who felt well completed the questionnaires. The ERG also commented that the lack of study blinding in COMBI-v may have influenced the scores reported by patients.

Cost effectiveness

- 3.10 The company presented a de novo partitioned survival model to assess the cost-effectiveness of trametinib plus dabrafenib in people with BRAF V600 mutation-positive unresectable or metastatic melanoma. The perspective was that of the NHS and personal social services. The time horizon of the model was life time (30 years), the cycle length was 1 week and half-cycle correction was not applied. Costs and outcomes were discounted at 3.5% per year. The model included 3 states: progression-free, post-progression and death. The company assumed that people

entered the model in the progression-free state and had treatment with trametinib plus dabrafenib or with one of the BRAF-inhibitor monotherapies (dabrafenib or vemurafenib). Transition between states was derived from response to treatment and risk of disease progression or death. Patients that transitioned to a post-progression state were assumed to discontinue therapy and they stayed in that state until transitioning to death. Progression of disease was defined using Response Evaluation Criteria in Solid Tumours (RECIST criteria, version 1.1).

- 3.11 The clinical-effectiveness estimates for each of the treatment groups were taken from pooled PFS and OS times at the final cut-off points from COMBI-v and COMBI-d. To estimate long-term PFS the company used Kaplan-Meier analysis until a set breakpoint (estimated using the piecewise linear function). Beyond the set breakpoint an assumption of constant hazards was applied to each group separately. This assumed that observed the PFS benefits would continue beyond the trial follow up. To estimate long-term OS the company used Kaplan-Meier data until a set breakpoint (estimated as above), after which an assumption of constant hazards was applied until year 5. After year 5, the company combined exponential extrapolation of constant hazards with long-term survival data from the American Joint Committee on Cancer (AJCC) registry, with case-mix adjustment by melanoma stage in each treatment group. General population mortality, matched by age and gender, was added to the AJCC rates after 20 years to account for increased risk of death in the population.
- 3.12 The company assigned utility values to each of the health states in the model using EQ-5D data from COMBI-v and COMBI-d. The model assumed that within each health state the quality of life is constant over time, i.e. a single utility value applies to that health state. Adverse events were indirectly incorporated in the model because utility data were taken directly from the trials. The model included all data on healthcare resource use associated with treatment and disease progression. The company

used the UK MELODY study (a study of resource utilisation in 220 people with melanoma) to inform UK clinical practice in melanoma treatment and for costing additional resource use in pre- and post-progression health states. Costs were inflated to current price levels. The model included post-study anti-cancer treatment costs, calculated as a weighted sum of the expected total post-study anti-cancer treatment cost per patient. Results from COMBI-d showed that a higher proportion of patients had a subsequent anti-cancer treatment after progression in the monotherapy group, compared with those who had trametinib plus dabrafenib (51% and 33% respectively). The differences in post-study treatments resulted in a difference in expected mean costs in each treatment group. The model incorporated costs of treating adverse events which the company determined were likely to have the greatest impact on NHS resource. This was derived by selecting those grade 3 and above adverse events with an incidence of 5% or over in each treatment group of COMBI-v or COMBI-d.

3.13 The company presented the results from the cost-effectiveness analysis based on the list prices of the intervention and comparator technologies. Results showed that trametinib plus dabrafenib was associated with a greater number of quality-adjusted life years (QALYs) compared with the monotherapies (1.345 more QALYs than vemurafenib and 1.298 more QALYs than dabrafenib). Because trametinib, dabrafenib and vemurafenib have confidential patient access schemes, the incremental cost-effectiveness ratios (ICERs) presented are not reflective of the actual cost to the NHS.

3.14 The company did deterministic sensitivity analysis varying the assumptions in the model. Results were sensitive to the time horizon of the model, with a longer time horizon reducing the ICERs for trametinib plus dabrafenib compared with the monotherapies. The company also reported that there was a reduction in the ICERs if an assumption of no continuing benefit for PFS beyond trial follow up was applied (that is, the treatment effect of combination therapy on progression disappears after the end of the trial period and, in the projection phase, if the monthly

hazards of progression were the same for combination therapy and monotherapy).

Evidence review group comments

- 3.15 The ERG commented that by pooling the data from COMBI-d and COMBI-v the company had not taken into account the potential for trial design bias. Although there were similarities in the trial designs and patient populations, COMBI-d was blinded and placebo controlled, while COMBI-v was not blinded and no placebo control was used. The ERG noted that the 2 trials have different survival profiles and considered that it was not appropriate to pool the data. It considered that the results from the high-quality, blinded placebo-controlled trial were more likely to show the true effectiveness of dabrafenib and vemurafenib, if their clinical equivalence was accepted.
- 3.16 The ERG did not consider that the company had appropriately extrapolated long-term OS. It considered that it was preferable to use all of the available trial data, rather than extrapolation, over a period for which data exists. It also noted that constant mortality hazards were not applied up to year 5 in the model, but up to month 30 (trametinib plus dabrafenib) or month 31 (monotherapy). The monthly mortality hazards declined in both groups consistently until they converged with the mortality hazards at year 5, underestimating the survival in the monotherapy arm.
- 3.17 The ERG noted that the mean time for patients to continue having treatment after investigator-assessed progression was over 200 days in the trametinib plus dabrafenib group. The ERG considered that PFS is a poor proxy for time on treatment and treatment costs, and that time to treatment discontinuation would provide a more accurate measure.
- 3.18 The ERG did not agree that post-study anti-cancer therapy costs were different between the treatment groups or that a simple average of the post-study anti-cancer therapy costs should be applied. The ERG noted that the company's post-study anti-cancer therapy costs did not represent

the current clinical pathway because less than 7% of patients in COMBI-d and COMBI-v had pembrolizumab.

- 3.19 The ERG noted that utility values used in the model were derived from the full study population and considered that data from European patients would provide a more representative estimate of health-related quality of life. It also considered the use of utility values from COMBI-v to be inappropriate considering the open label design of the trial. The ERG commented that it did not consider that there was a statistical reason to assume different utility values for dabrafenib and vemurafenib monotherapies compared with trametinib plus dabrafenib. It considered that it would be more meaningful to apply utility values that are related to being 'on' or 'off' study treatment as determined by the time to treatment discontinuation data. The ERG also considered that the utility values used in the model should reflect declining utility with age.

Evidence review group exploratory analyses

- 3.20 Using the company's model, the ERG presented deterministic cost-effectiveness results based on the confidential patient access scheme discounted prices of the intervention and comparator technologies. Because the patient access schemes are confidential, ICERs cannot be presented.
- 3.21 The ERG made several amendments to the company's model:
- using time to treatment discontinuation data to estimate study treatment costs
 - using equal post-study anti-cancer treatments for the intervention and comparator therapies
 - applying on and off treatment utility values relating to European patients and adjusted for age
 - applying the ERG's method for estimating OS
 - using COMBI-d trial data (instead of pooled data) and applying the ERG's preferred method for estimating OS.

Each amendment increased the incremental costs and the ICERs for trametinib plus dabrafenib compared with dabrafenib or vemurafenib alone. Applying the ERG's preferred method of extrapolating OS reduced the number of QALYs gained for trametinib plus dabrafenib from 1.297 QALYs to 0.878 QALYs compared with dabrafenib alone, and from 1.345 QALYs to 0.925 QALYs compared with vemurafenib alone.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of trametinib in combination with dabrafenib, having considered evidence on the nature of unresectable or metastatic BRAF V600 mutation-positive melanoma and the value placed on the benefits of trametinib plus dabrafenib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

- 4.1 The committee discussed the clinical need of people with unresectable or metastatic BRAF V600 mutation-positive melanoma. It heard from the patient experts that advanced melanoma can be associated with both disease-related symptoms and adverse effects from treatment, and the disease has a major impact on quality and length of life. It also heard that patients welcomed the combination of trametinib and dabrafenib, which they considered to be an effective and well tolerated new treatment. The committee concluded that the availability of a new combination treatment that slows disease progression and improves quality of life is very important to patients and their families.
- 4.2 The committee considered the current clinical management of unresectable and metastatic melanoma, and the potential place of trametinib plus dabrafenib in the pathway of care. It acknowledged that the management of advanced melanoma is changing rapidly with the availability of new immunotherapy and other treatments. It heard from the

clinical experts that immunotherapy agents are thought to have a very long-lasting effect in some people and there is emerging evidence that some people may also obtain long-term benefit from BRAF-specific therapy, although typically resistance to these agents develops relatively early. Survival data for various combination therapies is still immature, but they show promising survival gains compared with monotherapies. The committee understood from the clinical experts that trametinib plus dabrafenib would be used in place of BRAF-inhibitor monotherapy as the standard of care in 2 groups of patients with BRAF mutation-positive disease; previously untreated melanoma in patients with features such as high-volume disease, high serum LDH, rapid disease progression, poor performance status or brain metastases, or for those in whom the disease has progressed after immunotherapy. The committee concluded that trametinib plus dabrafenib is expected to replace the use of BRAF-inhibitor monotherapies in clinical practice, but that the evolving nature of the management of advanced melanoma made it difficult to determine its precise positioning in the pathway of care.

- 4.3 The committee discussed the generalisability of the clinical evidence presented in the company's submission from COMBI-d and COMBI-v, noting that there were several issues to consider. Firstly, in both trials, patients had not had previous treatment for unresectable or metastatic BRAF V600 mutation-positive melanoma. In addition, patients had a high performance status (ECOG status of 0 or 1) and fewer than 20 patients had brain metastases. The committee recalled the clinical experts' evidence (see section 4.2) that these characteristics did not fully reflect the groups of people for whom trametinib plus dabrafenib would be recommended in clinical practice. The clinical experts highlighted that the pivotal trials of BRAF-inhibitor monotherapies had also included only patients with previously untreated melanoma, but extensive subsequent clinical experience suggested that their efficacy was unaffected by prior immunotherapy. Therefore, they could infer that this would also be the case when BRAF inhibitors were used in combination with a MEK

inhibitor. The committee also heard from the clinical experts that there is no biological reason why trametinib plus dabrafenib would be relatively less effective in patients with a poorer performance status. The committee considered that in clinical practice some people would have a lower performance status than those in the trials, and that some would have previously had treatment with immunotherapy. However, it was prepared to accept that the results from the trials were broadly generalisable to the patients who would be offered the treatment in practice.

- 4.4 The committee examined the results from COMBI-d and COMBI-v. It noted that trametinib plus dabrafenib increased median progression-free survival by a statistically significant 2.2 months compared with dabrafenib and by 5.3 months compared with vemurafenib. It also acknowledged that trametinib plus dabrafenib increased median overall survival by a statistically significant 6.4 months compared with dabrafenib alone, and by 7.6 months compared with vemurafenib alone. The committee concluded that trametinib plus dabrafenib was clinically effective compared with the BRAF-inhibitor monotherapies.
- 4.5 The committee discussed the differences between COMBI-d and COMBI-v and the company's approach to pooling the efficacy data. It noted that COMBI-d was blinded and placebo controlled whereas COMBI-v was open label without a placebo control, which the ERG considered could introduce bias. However, the committee agreed that the primary outcome in COMBI-v was overall survival which would not be subject to bias. The committee was aware that the ERG did not consider it appropriate to pool the data from the 2 trials. The committee recalled that vemurafenib and dabrafenib had been accepted to have similar health benefits in previous NICE appraisals. It concluded that the trials were not sufficiently different for the pooling of the efficacy data to be unreasonable.
- 4.6 The committee considered the adverse events associated with trametinib plus dabrafenib. It was mindful of the recent Medicines and Healthcare products Regulatory Agency (MHRA) warning advising its use with

caution in people with risk factors for gastrointestinal perforation. It was also mindful of the ERG's comments that withdrawal rates from both trials due to adverse events were higher in the combination groups than in the monotherapy groups. However, it was told by the clinical experts that this could have been due to the design of the research protocol and would not be expected in clinical practice. The committee heard from the clinical experts that the main adverse effect specifically associated with trametinib plus dabrafenib was pyrexia, which would have led to immediate admission to hospital at the time of the trials, but is now understood to be unrelated to neutropenic sepsis and is usually managed satisfactorily without hospital admission. The committee was reassured by the patient and clinical experts that the adverse events associated with trametinib plus dabrafenib were generally tolerable, serious treatment-related adverse events were rare, and that it has a lower incidence of skin related toxicities compared with monotherapy. The committee concluded that trametinib plus dabrafenib has a manageable adverse event profile.

4.7 The committee examined the data presented on health-related quality of life in the company's submission. It noted with approval that the company had collected quality of life data in the trials, and that rates of completion were high. Data had been gathered using EQ-5D and other instruments. The committee noted that quality of life data had been collected in a number of different countries because of the multicentre design of the trials. There were some UK patients enrolled in the trials, but it was uncertain whether the whole trial data would apply to the population treated in England. The committee concluded that the data had come directly from participants in the trials who had received the treatments, and there was no evidence to suggest that the health-related quality of life data from the trials was not generalisable to patients in England.

4.8 The committee considered the likely duration of therapy with trametinib plus dabrafenib, noting that the trials and the marketing authorisation permitted its use beyond disease progression if the patient was still receiving benefit. However, the committee heard from the clinical experts

that given the choice of alternative therapies now available patients would generally be offered an alternative treatment at the time of disease progression, and the committee accepted that this was likely. The committee also noted that a higher percentage of people in the monotherapy groups had post-progression treatment compared with those having trametinib plus dabrafenib. However, the committee concluded that, because clinical practice is changing, it was not known whether this difference would also be seen in clinical practice.

Cost effectiveness

- 4.9 The committee considered the company's modelling of cost effectiveness. It noted that it used a 3 state partitioned model structure, which the company stated had been used in previous NICE appraisals. It also noted the ERG's concern that this type of model structure produces counterintuitive results whereby the less effective the intervention is assumed to be at delaying progression, the more cost effective it becomes. The committee understood that this reflects the lack of a direct modelled relationship between progression-free survival and overall survival. The committee agreed that the ERG's comments were worthy of note, but concluded that the model was in line with accepted NICE methods and was therefore appropriate for decision making.
- 4.10 The committee examined the modelling of overall survival, noting that the ERG had raised several concerns about the company's modelling method. When the ERG used an alternative method of modelling, its estimate for trametinib plus dabrafenib was very similar to the company's. For the control group, however, the ERG's estimate for overall survival was higher than that estimated by the company and it considered the company's estimate of survival at 5 years to be implausible. The committee heard from the company that it had estimated that 14% of people in the control group would be alive at 5 years, and that this was not implausible taken in the context of what is known about survival in advanced melanoma. However, the committee acknowledged that the

ERG had used the totality of the observed Kaplan-Meier data available from the trials, which the company had not, and had used a less complex method of extrapolation using mortality hazard rates from the American Joint Committee on Cancer (AJCC) registry, and that this approach appeared reasonable. The committee concluded that there were uncertainties in modelling of overall survival which required long-term extrapolation of data beyond the end of the trial. Although the ERG's approach made more use of the available trial data, it was unclear which method produced the more plausible results.

- 4.11 The committee considered whether the costs included in the model were appropriate. It noted the ERG's view that the company's method of using progression-free survival data to estimate treatment cost underestimated the true costs because over a quarter of patients in both trials continued on treatment post-progression. It understood that the ERG considered that time to treatment discontinuation provided a better estimate. The committee recalled the comments from the clinical experts (see section 4.8) that patients tended to switch treatment at the time of progression because of the availability of other treatments. Therefore it concluded that the company's approach to estimating costs using progression free survival was acceptable.
- 4.12 The committee also considered the ERG's opinion that the company had inappropriately assumed different post-study anti-cancer treatment costs for the combination and monotherapy groups. The committee considered that there was considerable uncertainty about the treatments given post progression, and the associated costs. In the absence of evidence to the contrary, it was minded to accept the data from the trials which showed some differences in costs between the treatment groups.
- 4.13 The committee considered the quality of life data used in the cost effectiveness modelling. It appreciated that there were different ways of incorporating quality of life values into the model; for example, using the full EQ-5D dataset from the trials or a subset of European patients in line

with the ERG's preferred approach. The committee noted that the ERG also favoured using equivalent quality-of-life estimates for both treatment groups in the pre-progression health state rather than lower values for the monotherapies. However, given that the data had been gathered directly in the trials, showed some statistically significant differences between the treatment groups, and that regional differences were uncertain, the committee preferred to use the quality of life data directly from the trials.

4.14 The committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.

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

In addition, when taking these criteria into account, the committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.15 The Committee discussed whether trametinib plus dabrafenib met all the criteria to be considered a life-extending, end-of-life treatment. It accepted that there is sufficient evidence to indicate that the treatment offers an extension to life of at least 3 months compared with current NHS treatment. It also accepted that the patient population for unresectable or metastatic BRAF V600 mutation-positive melanoma is small (approximately 1,000 patients annually). The committee recognised that

median overall survival in the monotherapy groups of the trials was less than 24 months, but that the modelled mean survival was more than 24 months. The committee appreciated that the difference in median and mean survival estimates may reflect the small number of people who survive many years with this condition, and did so even before effective treatments were available as demonstrated in the AJCC registry. It considered that as treatment for advanced melanoma improves, overall survival is likely to increase to more than 24 months. However, the committee concluded that trametinib plus dabrafenib currently met all the criteria to be considered a life-extending end-of-life treatment.

4.16 The committee examined the cost-effectiveness estimates which incorporated the confidential patient access schemes for trametinib plus dabrafenib and for dabrafenib or vemurafenib alone. It recalled that there were uncertainties regarding the modelling of overall survival and considered that while the most plausible incremental cost-effectiveness ratio (ICER) was uncertain, it would be no higher than the ERG's estimate using its preferred method of modelling. Taking together all the evidence and uncertainties, and given the extra weight applied to quality-adjusted life years (QALYs) at the end of life, the committee agreed that the estimates presented by the ERG and the company were within the range normally considered a cost effective use of NHS resources. It concluded that trametinib plus dabrafenib could therefore be recommended as a treatment option for people with unresectable or metastatic BRAF V600 mutation-positive melanoma.

4.17 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the

PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

4.18 The committee discussed the innovative aspects of trametinib in combination with dabrafenib. It accepted that the combination therapy has shown substantial efficacy gains, without any increase in adverse effects, and indeed reduces the incidence of a number of skin toxicities associated with BRAF inhibitor therapy. In those respects the committee agreed with the company that it could be considered innovative. However, it could not identify any health-related benefits that had not been already captured in the QALY calculation.

Summary of appraisal committee’s key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
Trametinib in combination with dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic melanoma in adults with a BRAF V600 mutation, only when the company provides trametinib and dabrafenib with the discounts agreed in the patient access schemes.		1.1
<ul style="list-style-type: none"> The committee concluded that trametinib plus dabrafenib was clinically effective compared with the BRAF inhibitor monotherapies. 		4.4
<ul style="list-style-type: none"> The committee considered that while the most plausible incremental cost-effectiveness ratio (ICER) was uncertain, it would be no higher than the evidence review group (ERG’s) estimate using its preferred method of modelling overall survival. Taking together all the evidence and uncertainties, and given the extra weight applied to quality-adjusted life years (QALYs) at the end of life, the committee concluded that the estimates presented by the ERG and the company were within the range normally considered a cost effective use of NHS resources. 		4.16

<ul style="list-style-type: none"> The committee concluded that trametinib plus dabrafenib currently met all the criteria to be considered a life-extending end-of-life treatment. 	4.15	
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee concluded that the availability of a new combination treatment that slows disease progression and improves quality of life is very important to patients and their families.	4.1
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee accepted that the combination therapy has shown substantial efficacy gains, without any increase in adverse effects, and reducing the incidence of a number of skin toxicities associated with BRAF-inhibitor therapy. In those respects it could be considered innovative.	4.18
What is the position of the treatment in the pathway of care for the condition?	The committee concluded that trametinib plus dabrafenib was expected to replace the use of BRAF-inhibitor monotherapies in clinical practice, but that the evolving nature of the management of advanced melanoma made it difficult to determine its precise positioning in the pathway of care.	4.2
Adverse reactions	The committee concluded that trametinib plus dabrafenib has a manageable adverse event profile.	4.6

Evidence for clinical effectiveness		
<p>Availability, nature and quality of evidence</p>	<p>The company identified 2 phase III randomised controlled trials (COMBI-d and COMBI-v) that assessed the clinical effectiveness of trametinib plus dabrafenib in people with histologically-confirmed stage IIIC (unresectable) or stage IV (metastatic) BRAF V600E/K mutation-positive melanoma.</p> <p>The ERG considered COMBI-d to be well designed and to have a low risk of bias. It reported that COMBI-v was of good quality but that the trial was open-label and did not include a placebo control or a blinded independent review of the secondary outcomes, which could lead to bias.</p> <p>The committee agreed that the primary outcome in COMBI-v was overall survival, which would not be subject to bias.</p>	<p>3.1</p> <p>3.8</p> <p>4.5</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The committee considered that in clinical practice some people would have a lower performance status than those in the trials, and that some would have had immunotherapy previously. However, it was prepared to accept that the results from the trials were broadly generalisable to the patients who would be offered the treatment in practice.</p> <p>The committee concluded that there was no evidence to suggest that the health-related quality of life data from the trials was not generalisable to patients in England.</p>	<p>4.3, 4.7</p>

<p>Uncertainties generated by the evidence</p>	<p>No other uncertainties were identified.</p>	<p align="center">–</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>None were identified.</p>	<p align="center">–</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The committee noted that trametinib plus dabrafenib increased median progression-free survival by a statistically significant 2.2 months compared with dabrafenib alone and by 5.3 months compared with vemurafenib alone.</p> <p>The committee acknowledged that trametinib plus dabrafenib increased median overall survival by a statistically significant 6.4 months compared with dabrafenib alone and by 7.6 months compared with vemurafenib alone.</p> <p>The committee concluded that trametinib plus dabrafenib was clinically effective compared with the BRAF-inhibitor monotherapies.</p>	<p align="center">4.4</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The committee concluded that the company's 3 state partitioned model was in line with accepted NICE methods and was therefore appropriate for decision making.</p>	<p align="center">4.9</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The committee concluded that there were uncertainties in the modelling of overall survival which required long term extrapolation of data beyond the end of the trial. The committee acknowledged that the ERG had used the totality of the observed Kaplan-Meier data available from the trials, which the company had not, and had used a less complex method of extrapolation using mortality hazard rates from the American Joint Committee on Cancer registry, and that this approach appeared reasonable. The committee concluded that the ERG’s approach made more use of the available trial data, but it was unclear which method produced the more plausible results.</p>	<p>4.10</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The committee appreciated that there were different ways of incorporating quality of life values into the model, for example using the full EQ-5D dataset from the trials or a subset of European patients in line with the ERG’s preferred approach. Given that the data had been gathered directly in the trials, showed some statistically significant differences between the treatment groups, and that regional differences were uncertain, the committee preferred to use the quality of life data directly from the trials.</p> <p>The committee could not identify any health-related benefits that had not been already captured in the quality-adjusted life year (QALY) calculation.</p>	<p>4.13</p> <p>4.18</p>

Are there specific groups of people for whom the technology is particularly cost effective?	No subgroups were identified.	–
What are the key drivers of cost effectiveness?	The committee concluded that there were uncertainties in modelling of overall survival which required long-term extrapolation of data beyond the end of the trial. Although the ERG’s approach made more use of the available trial data, it was unclear which method produced the more plausible results.	4.10
Most likely cost-effectiveness estimate (given as an ICER)	The committee considered that while the most plausible ICER was uncertain, it would be no higher than the ERG’s estimate using its preferred method of modelling overall survival. The committee agreed that the estimates presented by the ERG and the company were within the range normally considered a cost effective use of NHS resources.	4.16
Additional factors taken into account		
Patient access schemes (PPRS)	Recommended with the discount agreed in the patient access schemes for trametinib and dabrafenib.	1.1
End-of-life considerations	The committee concluded that trametinib plus dabrafenib currently met all the criteria to be considered a life-extending end-of-life treatment.	4.15

<p>Equalities considerations and social value judgements</p>	<p>No equalities issues were identified.</p>	<p>–</p>
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5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has unresectable or metastatic melanoma with a BRAF V600 mutation and the doctor responsible for their care thinks that trametinib plus dabrafenib is the right treatment, it should be available for use, in line with NICE’s recommendations.
- 5.4 The Department of Health and Novartis Pharmaceuticals have agreed that trametinib and dabrafenib will be available to the NHS with patient access schemes which make them available with a discount. The size of the discounts are commercial in confidence. It is the responsibility of the company to communicate details of the discounts to the relevant NHS

organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [\[NICE to add details at time of publication\]](#)

6 Related NICE guidance

Further information is available on the [NICE website](#).

Published

- [Nivolumab for treating advanced \(unresectable or metastatic\) melanoma](#) (2016) NICE technology appraisal guidance 384
- [Pembrolizumab for advanced melanoma not previously treated with ipilimumab](#) (2015) NICE technology appraisal guidance 366
- [Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab](#) (2015) NICE technology appraisal guidance 357
- [Melanoma: assessment and management](#) (2015) NICE guideline 14
- [Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma](#) (2014) NICE technology appraisal guidance 321
- [Ipilimumab for previously untreated advanced \(unresectable or metastatic\) melanoma](#) (2014) NICE technology appraisal guidance 319
- [Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma](#) (2013) NICE interventional procedure guidance 446
- [Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma](#) (2012) NICE technology appraisal guidance 269
- [Ipilimumab for previously treated advanced \(unresectable or metastatic\) melanoma](#) (2012) NICE technology appraisal guidance 268
- [Skin cancer prevention: information, resources and environmental changes](#) (2011) NICE public health guideline 32
- [Improving outcomes for people with skin tumours including melanoma](#) (2010) NICE guideline CSG88

Under development

- [Cobimetinib with vemurafenib for treating advanced, unresectable or metastatic BRAF V600 mutation-positive melanoma](#). NICE technology appraisal guidance (publication expected June 2016)
- [Talimogene laherparepvec for treating metastatic melanoma](#). NICE technology appraisal guidance (publication expected July 2016)
- [Skin cancer](#). NICE quality standard (publication expected August 2016)

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam

Chair, appraisal committee

April 2016

8 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The appraisal committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. There are 4 appraisal committees, each with a chair and vice chair. Each appraisal committee meets once a month, except in December when there are no meetings. Each committee considers its own list of technologies, and ongoing topics are not moved between committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)

Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice Chair)

Consultant Physician, University Hospitals of Leicester

Dr Graham Ash

Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Professor Aileen Clarke

Professor of Public Health & Health Services Research, University of Warwick

Dr Justin Daniels

Consultant Paediatrician, North Middlesex University Hospital

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Mr Adrian Griffin

Vice President, HTA & International Policy, Johnson & Johnson

Dr Rachel Hobson

Formulary Pharmacist, NHS Wiltshire Clinical Commissioning Group

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Mohit Misra

GP, Queen Elizabeth Hospital, London

Ms Pamela Rees

Lay Member

Ms Ellen Rule

Director of Transformation and Service Redesign, Gloucestershire Clinical
Commissioning Group

Mr Stephen Sharp

Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Mr David Thomson

Lay member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University and Consultant in Public Health Medicine,
National Public Health Service Wales

Dr Nerys Woolacott

Senior Research Fellow, Centre for Reviews and Dissemination, University of York

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health
technology analysts (who act as technical leads for the appraisal), a technical
adviser and a project manager.

Henry Edwards

Technical Lead

Zoe Charles

Technical Adviser

Bijal Joshi

Project Manager

9 Sources of evidence considered by the committee

A. The evidence review group (ERG) report for this appraisal was prepared by Liverpool Reviews & Implementation Group (LRiG):

- Greenhalgh J, Mahon J, Beale S, et al., Trametinib in combination with dabrafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID661]: A Single Technology Appraisal, February 2016

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions.

Organisations listed in II gave their expert views on trametinib in combination with dabrafenib by making a submission to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I. Company:

- Novartis Pharmaceuticals (trametinib and dabrafenib)

II. Professional/specialist and patient/carer groups:

- British Association of Dermatologists
- British Association of Skin Cancer Specialist Nurses
- Cancer Research UK
- Melanoma Focus
- Melanoma UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- UK Clinical Pharmacy Association

III. Other consultees:

National Institute for Health and Care Excellence

Final appraisal determination – [appraisal name]

Issue date: [month year]

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Roche Products (vemurafenib)

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on trametinib and dabrafenib by providing oral evidence to the committee.

- Mrs Jackie Hodgetts, Nurse Clinician, nominated by organisation representing British Association of Skin Cancer Specialist Nurses – clinical expert
- Dr Paul Nathan, Consultant Medical Oncologist, nominated by organisation representing Melanoma Focus – clinical expert
- Dr Pippa Corrie, Consultant Medical Oncologist, nominated by organisation representing the Royal College of Physicians – clinical expert
- Mrs Gillian Nuttall, nominated by organisation representing Melanoma UK – patient expert

D. Representatives from the following company attended committee meetings. They contributed only when asked by the committee chair to clarify specific issues and comment on factual accuracy.

- Novartis Pharmaceuticals

ISBN: [to be added at publication]