Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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trametinib 0.5mg and 2mg film-coated tablets (Mekinist®) SMC No. (1161/16)

Novartis Pharmaceuticals UK Ltd

05 August 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and ultra-orphan medicine process

trametinib (Mekinist®) is accepted for restricted use within NHS Scotland.

Indication under review: in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

SMC restriction: to first-line treatment.

In two phase III studies, trametinib in combination with dabrafenib improved progression-free survival and overall survival compared with BRAF inhibitor monotherapy for the first-line treatment of unresectable or metastatic melanoma with BRAF V600 mutation in adults.

This advice takes account of the benefits of Patient Access Schemes (PAS) that improve the cost-effectiveness of trametinib and dabrafenib. This advice is contingent upon the continuing availability of these patient access schemes in NHS Scotland or list prices that are equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Trametinib is also licensed as monotherapy. As the company submission related only to combination therapy, SMC cannot recommend use as monotherapy.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Trametinib is licensed in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

(Dabrafenib is licensed as monotherapy or in combination with trametinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.)

Dosing Information

Trametinib 2mg orally once daily with a full glass of water. Tablets should not be chewed or crushed. Trametinib should be taken without food, at least one hour before or two hours after a meal and at a similar time every day, with either the morning or evening dose of dabrafenib.

Dabrafenib 150mg orally twice daily (approximately 12 hours between doses). Refer to the dabrafenib summary of product characteristics (SPC) for details.

It is recommended that patients continue treatment until patients no longer derive benefit or the development of unacceptable toxicity.

See SPC for information on dose modifications for adverse events.

Before taking trametinib and dabrafenib, patients must have confirmation of BRAF V600 mutation using a validated test.

Treatment with trametinib and dabrafenib should be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.

Product availability date

November 2015.
Trametinib in combination with dabrafenib meets SMC end of life and ultra-orphan criteria.

Background

Trametinib is a first-in-class reversible, selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. This extracellular signal-related kinase (ERK) pathway is often activated by mutated forms of BRAF in melanoma and other cancers. Dabrafenib is a protein kinase inhibitor. Use of trametinib in combination with dabrafenib provides dual inhibition of the ERK pathway.[1,2]

The submitting company has requested that SMC considers the use of trametinib in combination with dabrafenib in the first-line treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. Trametinib is also licensed as monotherapy; this submission relates to combination therapy only.

Trametinib in combination with dabrafenib meets SMC end of life and ultra-orphan criteria.

Nature of condition

A patient and clinician engagement (PACE) meeting was held to consider the added value of trametinib in combination with dabrafenib in the context of treatments currently available in NHS Scotland. PACE participants highlighted that advanced melanoma is an aggressive and debilitating disease which commonly affects a younger population. The majority of patient have multiple metastases and decline rapidly. Patients develop incapacitating symptoms, such as bowel symptoms and difficulty in sleeping, which can affect normal daily activities and limit their ability to work and to care for young families. Patients may develop brain and bone metastases causing severe headaches, muscle pain and fractures with a resultant deterioration in quality of life.

Current treatment depends on BRAF mutational status: those with BRAF mutation are treated with first-line targeted therapy (dabrafenib or vemurafenib), and those without BRAF mutation with immunotherapy (ipilimumab, pembrolizumab or nivolumab). The benefit of BRAF or MEK inhibitor monotherapy appears to be limited by the development of resistance, with about half of patients progressing within 5 to 7 months. Combining trametinib and dabrafenib inhibits two kinases in the ERK pathway and potentially postpones or prevents the development of resistance.

Dabrafenib and vemurafenib are both BRAF inhibitors indicated as oral monotherapy treatment for adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation and both have been accepted by SMC, restricted to first-line use.

Impact of new technology

Summary of evidence on comparative efficacy

The evidence comes from two similar randomised, controlled phase III studies in previously untreated patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.[3-9] COMBI-d was a double-blind comparison of trametinib plus dabrafenib with dabrafenib alone in 423 patients.[3,4,5] COMBI-v was an open-label comparison of trametinib plus dabrafenib with vemurafenib in 704 patients.[3,7,8] Eligible patients in both studies were aged at least 18 years with histologically confirmed melanoma of either Stage IIIC (unresectable) or Stage IV (metastatic) and centrally confirmed BRAF V600E/K mutation status. They had measurable disease with at least one measurable lesion according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were randomised equally to receive trametinib (2mg orally once daily) plus dabrafenib (150mg orally twice daily) or dabrafenib (150mg orally twice daily) in COMBI-d, or vemurafenib (960mg orally twice daily) in COMBI-v. Randomisation was stratified by baseline lactate dehydrogenase (LDH) levels (>upper limit of normal [ULN] or ≤ULN) and by BRAF genotype (V600K or V600E). Study treatments continued until disease progression, unacceptable toxicity or patient refusal. Patients were allowed to continue study treatment after disease progression if they met specified criteria. After study discontinuation, patients could receive additional anti-cancer treatment at the discretion of the investigator. Crossover from dabrafenib to trametinib plus dabrafenib was not allowed in the COMBI-d study but was allowed from vemurafenib to trametinib plus dabrafenib in COMBI-v after the independent data monitoring committee (IDMC) had reviewed interim analysis results and recommended early stopping of the study.

In COMBI-d, the primary outcome was progression-free survival (PFS), defined as the time from randomisation to radiologic disease progression or death from any cause. This was assessed by the investigator according to RECIST version 1.1 criteria. At the time of the primary PFS analysis (cut-off

date August 2013), after a median follow-up of 9 months, median PFS was 9.3 months in trametinib plus dabrafenib patients versus 8.8 months in dabrafenib alone patients: adjusted hazard ratio 0.75 (95% confidence interval [CI]: 0.57 to 0.99), p=0.035.[3,4] At the January 2015 cut-off date, after a median follow-up of 20 months in the combination group and 16 months in the dabrafenib group, median PFS was 11.0 months versus 8.8 months respectively: adjusted hazard ratio 0.67 (95% CI: 0.53 to 0.84), p=0.0004.[5]

Secondary outcomes included overall survival (defined as the time from randomisation to death from any cause) and investigator-assessed overall response rate (ORR). At the August 2013 cut-off date, 19% (40/211) of trametinib plus dabrafenib patients and 26% (55/212) of dabrafenib alone patients had died and median overall survival had not been reached in either group: hazard ratio 0.63 (95% CI: 0.42 to 0.94), p=0.02. The pre-specified stopping boundary was not crossed and the study continued to final overall survival analysis (cut-off date January 2015), when 47% (99/211) and 58% (123/212) of patients respectively had died. Median overall survival was 25.1 months versus 18.7 months respectively: hazard ratio 0.71 (95% CI: 0.55 to 0.92), p=0.011. The treatment effect on PFS and overall survival was consistent across all pre-specified subgroups. At the August 2013 cut-off date, ORR was achieved by 67% (140/210) of trametinib plus dabrafenib patients and 51% (108/210) of dabrafenib alone patients with measurable disease at baseline: difference 16% (95% CI: 6% to 25%), p=0.002, with a complete response in 10% (22/210) and 8.6% (18/210) of patients respectively. At the January 2015 cut-off date, 69% (144/210) and 53% (112/210) of patients respectively had an ORR (difference 15% [95% CI: 6% to 24%], p=0.0014) and there was a complete response in 16% (33/210) and 13% (28/210) of patients respectively.[3,4,5]

In COMBI-d, quality of life was measured by the using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ C30), a generic assessment for cancer patients which includes five functional scales (physical, role, emotional, cognitive and social), one global health status scale, three symptom scales (fatigue, nausea and vomiting, and pain), and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). Results from the August 2013 cut-off date found significantly greater improvements from baseline in the trametinib plus dabrafenib versus dabrafenib alone group in global health scale at some timepoints. There was also a trend generally favouring trametinib plus dabrafenib in all functional scales which reached statistically significance at some timepoints. There were significantly greater improvements in the trametinib plus dabrafenib versus dabrafenib alone group in pain symptom score at all timepoints, and differences numerically favoured trametinib plus dabrafenib for fatigue and insomnia symptom scores, while nausea and vomiting, diarrhoea, dyspnoea, and constipation generally numerically favoured dabrafenib alone.[6]

In COMBI-v, the primary outcome was overall survival, and at the time of the pre-planned interim analysis (cut-off date April 2014), after a median follow-up of 11 months in the trametinib plus dabrafenib and 10 months in the vemurafenib group, 28% (100/352) of trametinib plus dabrafenib patients and 35% (122/352) of vemurafenib patients had died. Median overall survival had not been reached in the trametinib plus dabrafenib group and was 17.2 months in the vemurafenib group: adjusted hazard ratio 0.69 (95% CI: 0.53 to 0.89), p=0.005. Since the adjusted stopping boundary for efficacy at the interim analysis was crossed (p<0.0214), the IDMC recommended stopping the study early and this analysis was considered the final overall survival analysis.[3,7] An updated overall survival analysis (cut-off date March 2015) was performed after a median follow-up of 19 months when 44% (155/352) of trametinib plus dabrafenib patients and 55% (194/352) of vemurafenib patients had died; median overall survival was 25.6 months and 18.0 months respectively: adjusted hazard ratio 0.66 (95% CI: 0.53 to 0.81), p<0.001.[1,3,8]

Secondary outcomes included investigator-assessed PFS and ORR. At the April 2014 cut-off date, median PFS was 11.4 months in the trametinib plus dabrafenib group and 7.3 months in the vemurafenib group: adjusted hazard ratio of 0.56 (95% CI: 0.46 to 0.69), p<0.001. At the March 2015

cut-off date, median PFS was 12.6 months versus 7.3 months respectively: adjusted hazard ratio 0.61 (95% CI: 0.51 to 0.73), p<0.001. Subgroup analyses for overall survival and PFS found a generally consistent treatment effect across all pre-specified subgroups. At the April 2014 cut-off date, an ORR was achieved by 64% (226/351) of trametinib plus dabrafenib patients and 51% (180/350) of vemurafenib patients with measurable disease at baseline: difference 13% (95% CI: 5.7% to 20%), p=0.0005, with a complete response in 13% (47/351) and 7.7% (27/350) of patients respectively. At the March 2015 cut-off date, 66% (231/351) and 53% (186/350) of patients respectively had an ORR (difference: 13% [95% CI: 5.3% to 20%], p=0.0008), with a complete response in 17% (59/351) and 10% (36/350) of patients respectively.[7,8]

In COMBI-v, quality of life was measured by EORTC-QLQ C30, EQ-5D and the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) which includes the FACT-general questionnaire plus the Melanoma and Melanoma Surgery subscales. Results from the April 2014 cut-off date found significantly greater improvements from baseline in the trametinib plus dabrafenib versus vemurafenib group in EORTC-QLQ C30 global health scale and in physical, social and role functional scales at all timepoints, and at some timepoints for emotional and cognitive functioning. There were statistically significantly greater improvements in the trametinib plus dabrafenib versus vemurafenib group at all timepoints in symptom scores for pain, insomnia and appetite loss. Differences between trametinib plus dabrafenib and vemurafenib in mean EQ-5D thermometer and utility scores and in mean FACT-M subscale scores were significantly better and clinically meaningful at all timepoints.[9]

Summary of evidence on comparative safety

At January 2015 cut-off in COMBI-d, an adverse event had been reported in 97% (203/209) of trametinib plus dabrafenib patients and 97% (205/211) of dabrafenib alone patients, and these were considered to be treatment-related in 87% and 90%, and serious in 42% and 37% of patients respectively. An adverse event led to discontinuation of study drugs in 11% and 6.6% of patients respectively. The most frequently reported adverse events in the trametinib plus dabrafenib group and dabrafenib alone groups included pyrexia (57% and 33%), fatigue (39% and 37%), nausea (34% and 27%), headache (33% and 30%), chills (31% and 17%), diarrhoea (30% and 16%), rash (27% and 22%), arthralgia (26% and 31%), vomiting (25% and 14%), hypertension (25% and 16%), cough (21% each) and oedema peripheral (21% and 9.0%). were Other events of interest reported in trametinib plus dabrafenib and dabrafenib alone patients included dermatitis acneiform (8.1% and 3.3%), bleeding events (6.2% and 4.3%), decreased ejection fraction (4.3% and 3.3%), cutaneous squamous cell carcinoma (2.9% and 9.5%), blurred vision (1.9% each), non-cutaneous malignancies (1.0% and 1.9%), chorioretinopathy (0.5% each) and new primary melanoma (0.5% and 1.9%).[5] One treatment-related death was reported in the dabrafenib alone group.[3,5]

At March 2015 cut-off in COMBI-v, an adverse event had been reported in 99% (343/350) of trametinib plus dabrafenib patients and 99% (345/349) of vemurafenib patients. An adverse event led to discontinuation of study drugs in 16% and 14% of patients respectively. The most frequently reported adverse events in the trametinib plus dabrafenib group and vemurafenib groups included pyrexia (55% and 21%), nausea (36% and 37%), diarrhoea (34% and 39%), chills (33% and 8%), headache (32% and 24%),fatigue (31% and 34%), vomiting (31% and 16%), hypertension (29% and 23%), arthralgia (27% and 52%), rash (24% and 43%), cough (22% and 11%), myalgia (19% and 16%), asthenia (17% in each) and increased ALT (14% and 17%).[8]

Other events of interest reported in trametinib plus dabrafenib and vemurafenib patients included decreased ejection fraction (8.3% and 0%), dermatitis acneiform (6.3% and 5.7%), cutaneous squamous cell carcinoma (1.4% and 18%), non-cutaneous malignancies (0.9% and 0.6%), chorioretinopathy (0.6% and 0.3%) and new primary melanoma (0.6% and 2.0%). There were no treatment-related deaths in either group.[7]

In both studies, alopecia, palmar-plantar erythrodysaesthesia and events related to hyperproliferative states of the skin were less commonly with trametinib plus dabrafenib than dabrafenib or vemurafenib monotherapy.[3]

PACE participants noted that a lot of patients experience significant toxicity with monotherapy, particularly skin toxicities, and the development of hyperkeratosis and arthralgia may result in patients being unable to maintain their dabrafenib dosing schedule. The combination therapy results in significantly less skin toxicity.

Summary of clinical effectiveness issues

Evidence for the trametinib plus dabrafenib combination comes from two pivotal studies against relevant comparators, dabrafenib and vemurafenib. In COMBI-d, the primary outcome, PFS, was significantly longer in the trametinib plus dabrafenib group compared with dabrafenib alone, and in COMBI-v, the primary outcome, overall survival, was significantly longer in the trametinib plus dabrafenib group compared with vemurafenib. The European Medicines Agency (EMA) describes the results as clinically relevant. At the final analyses, dabrafenib plus trametinib was associated with an increase in median OS of about 6.4 months relative to dabrafenib in the COMBI-d study, and 7.6 months relative to vemurafenib in the COMBI-v study. The median increases in PFS were smaller.[3-9]

Post-progression treatments may have affected the survival results. After disease progression, patients meeting the specified criteria could remain on study treatment, and 29% of trametinib plus dabrafenib and 31% of dabrafenib patients in the COMBI-d study and 23% in each group of the COMBI-v study continued for at least 15 days. Subsequent anti-cancer treatments could also be used at the discretion of the investigator, and in COMBI-d, 33% and 51% of patients respectively and in COMBI-v, 34% and 51% respectively received further treatment. The COMBI-v study was stopped after results at the interim survival analysis crossed the pre-specified stopping boundary and patents could cross over from vemurafenib to trametinib plus dabrafenib. Only 6% of patients crossed over and the impact was tested using different adjustment methods with results consistent with the primary analysis.[3,5,7]

COMBI-v was of open-label design but since the primary outcome was overall survival, potential bias is minimal.[3,7]

Both studies excluded patients who had received previous anti-cancer treatment for stage III or IV disease. Although the licensed indication is for patients with unresectable or metastatic melanoma with a BRAF V600 mutation regardless of prior therapy, the company has positioned this combination treatment for first-line use and this reflects the evidence from the pivotal studies.

Both studies excluded patients with active brain metastases and the SPC notes that the safety and efficacy of trametinib plus dabrafenib has not been evaluated in patients with a BRAF V600 mutation-positive melanoma which has metastasised to the brain.[1]

Both studies excluded patients with a history or evidence of cardiovascular risk so the safety in this population is unknown.[1,3]

Both studies recruited patients with an ECOG performance status of 0 or 1 and the treatment effect may not be generalisable to patients with poorer performance status.

Trametinib has been reported to decrease left ventricular ejection fraction (LVEF) and the SPC notes that in clinical trials, the median time to onset of the first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease was between 2 and 5 months. It is recommended that trametinib is used with caution in patients with impaired left ventricular function. LVEF should be evaluated in all

patients before starting treatment with trametinib, one month after initiation of therapy, and then at approximately every three months during treatment.[1]

The SPC notes that haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, have occurred in patients taking trametinib as monotherapy and in combination with dabrafenib. The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, patients should be treated as clinically indicated.[1]

The incidence of adverse events with the combination was generally comparable to monotherapy and although slightly higher, they were manageable either through dose interruption or reduction. The greatest differences in incidences of adverse events were for pyrexia and chills, which were more frequently reported for patients treated with combination therapy than with dabrafenib or vemurafenib monotherapy. However, the incidence of squamous cell carcinoma and keratoacanthoma was lower in the combination than in the monotherapy groups of the COMBI-d and COMBI-v studies. The EMA notes that since the risk and actual occurrence of squamous cell carcinoma is an important additive burden for patients; therefore, a decrease in its incidence is considered an advantage of the combination therapy.[3]

The combination of trametinib plus dabrafenib provides an alternative oral treatment to BRAF inhibitor montherapy in patients with BRAF V600 mutation positive advanced melanoma. The combination has been associated with improved survival, improvements in quality of life and reductions in some adverse events associated with monotherapy. Clinical experts consulted by SMC considered that the combination of trametinib and dabrafenib is a therapeutic advancement due to improved survival outcomes.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of trametinib in combination with dabrafenib, as an end of life and ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Advanced melanoma is an aggressive and debilitating disease which commonly affects a younger population. The majority of patients have multiple metastases and develop incapacitating symptoms which can affect normal daily activities with a resultant deterioration in quality of life.

- Trametinib, in combination with dabrafenib, is a therapeutic advancement due to a higher response rate which provides an opportunity to extend overall survival.

- The combination regimen provides a further treatment option for patients which offers a more favourable toxicity profile with respect to some toxicities (including skin) compared to monotherapy.

- This oral treatment regimen provides benefits with respect to administration for patients, their families and the health service.

- Trametinib, in combination with dabrafenib has been shown to improve quality of life in addition to extending overall survival.

- This combination regimen is becoming the standard of care in other countries.

Additional patient and carer involvement
We received patient group submissions from Melanoma Action and Support Scotland (MASScot) and Melanoma UK. MASScot has not received any pharmaceutical company funding in the last two years. Melanoma UK has received 14% pharmaceutical company funding in the past two years, but none from the submitting company. A representative from both patient groups also participated in the PACE meeting. The keys points of their submissions have been included in the full PACE statement.

Value for money

The submitting company presented a cost-utility analysis comparing trametinib plus dabrafenib to either dabrafenib or vemurafenib for first-line treatment of patients with unresectable or metastatic BRAF V600 mutation-positive metastatic melanoma.

A partitioned survival model with 3 health states (PFS, progressed disease and death), over a lifetime horizon of 30 years was used. Clinical data came from pooled patient level data from the pivotal COMBI-v and COMBI-d studies, with the assumption that dabrafenib and vemurafenib have comparable efficacy. Extrapolation for PFS and overall survival (OS) used Kaplan-Meier data for each treatment arm until a break point, beyond which a long-term linear trend was assumed, with a constant hazard ratio. The OS rates at the end of follow-up were assumed to converge with those reported in an American Melanoma Registry by year 5. From years 5 to 20, OS survival probabilities from the Registry data were modelled using a restricted cubic spline curve. After 20 years, mortality was projected using age- and gender-matched general-population mortality rates, which were scaled up by 1.42 to account for the increased relative risk of mortality in this population. The relative benefit from trametinib plus dabrafenib compared to monotherapy was assumed to be maintained over the 30 year time horizon.

Utility values were taken from EQ-5D data collected in the clinical studies. This resulted in utility values of 0.837, 0.789 and 0.746 for progression-free patients on trametinib plus dabrafenib, dabrafenib and vemurafenib respectively. For the progressed disease state, a common utility value of 0.697 was used for all treatments.

Resource use related to medicine acquisition and administration costs, adverse event costs, background disease management costs and costs associated with subsequent lines of therapy. Adverse events were based on grade 3+ events with an incidence of >5% from the respective clinical studies, and resource use for each estimated using published data.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group as acceptable for implementation in NHS Scotland. Under the PAS, a discount is offered on the list price of trametinib. Existing PAS are in place for dabrafenib and vemurafenib and these were included in the analysis by using an estimate of the relevant prices.

Base case incremental cost effectiveness ratios (ICERs) for pairwise comparisons with the trametinib PAS are noted in the table below:

	Versus dabrafenib	Versus vemurafenib
Incremental cost	£45,596	£53,741
Incremental quality adjusted life year (QALY)	1.298	1.345
ICER	£35,134	£39, 956

A range of sensitivity analyses was presented which showed that, against both comparators, the results were sensitive to assuming no continuing benefit for PFS. This reduced the pairwise ICERs with PAS to £34,099 and £28,980 compared to vemurafenib and dabrafenib respectively. The reduced ICERS arose because the reduction in medication costs had a greater impact on ICERs than the reduced QALYs. ICERs were not sensitive to costs of managing disease progression, terminal care costs, 10 or 40 year time horizons and the utility decrements applied to dabrafenib and vemurafenib.

A number of weaknesses were noted with the analysis:

- Adoption of break points resulted in the use of data extrapolated from curves rather than the actual data on PFS and OS from the clinical studies for these points. For example, the extrapolation of OS for the monotherapies used less than 4 months of the reported OS data. However, results of a sensitivity analysis using a cut-point of 18 months for the OS projection for the monotherapy arms reduced the with-PAS ICERs to £35,854 and £31,507 versus vemurafenib and dabrafenib respectively. The company indicated that the use of the 4 month cut-points was less subjective as it was based on a maximum likelihood estimate.
- The utility value for the post-progression status was measured at 5 weeks post-assessment and generalised over the 30 year life of the model. However, utilities decline with age and as death approaches so this single value is may not be appropriate and may introduce some bias. Adopting a lower average utility value for the post- progression phase for all treatments would increase the ICERs.
- The modelled cumulative doses of vemurafenib were higher than those from the Combi-v study, partly as a result of the use of the pooled data to derive the PFS estimates. Adjusting modelled doses to reflect study doses increased the pair-wise with-PAS ICER for dabrafenib plus trametinib versus vemurafenib to £47,327.
- The extensive sensitivity analyses explored many of the parameters giving rising to uncertainty. A remaining concern arises from issues with generalisability from studies to Scottish practice. Factors of concern include baseline health, comorbidities such as brain metastases, performance status of participants, treatment beyond progression, role of investigators to maximise compliance and the fact that one study was open label. The impact of these factors on the results is unknown.

*Other data were also assessed but remain commercially confidential.**

Impact beyond direct health benefits and on specialist services

PACE participants highlighted that as the combination regimen has been shown to increase quality of life, and this may allow patients to continue to self-care and regain their independence. As the affected patient group includes parents of dependent children and carers of elderly parents/relatives, this may allow them to regain their role as the main carer in their family or may allow patients of working age to return to work.

They noted that this oral regimen which can be taken at home, is convenient and allows greater patient independence. Of key importance is that patients can begin treatment immediately once it has been prescribed rather than having to wait for a number of weeks for a treatment slot for intravenous (IV) treatment. Oral therapy is less disruptive to patients and their families than IV therapy and it also avoids pressure on IV treatment slots, benefitting the service.

In addition, the further clinical benefits of the combination oral treatment may also delay the need for second-line intravenous infusion therapy with its associated costs for patients, their carers and the service.

At PACE it was reported that the improved tolerability of the combination regimen, particularly in terms of skin toxicity, may reduce the impact on dermatology and pathology as patients develop fewer lesions requiring local surgery.

Costs to NHS and Personal Social Services

The submitting company estimated the population eligible for treatment to be 91 patients per year, with an estimated uptake of 28% in year 1, rising to 42% in year 5.

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

Conclusion

The Committee also considered the benefits of trametinib plus dabrafenib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission and a substantial improvement in quality of life. In addition, as trametinib plus dabrafenib also meets SMC ultra-orphan criteria, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted trametinib plus dabrafenib for restricted use in NHS Scotland.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published a guideline on Melanoma: assessment and management of melanoma on 29 July 2015.[10] For systemic anticancer treatment this recommends targeted treatment with dabrafenib and vemurafenib as options for treating unresectable or metastatic BRAF V600 mutant positive melanoma and immunotherapy with ipilimumab as an option for treating unresectable or metastatic melanoma that has been previously treated or not. These agents are recommended only if manufacturers provide them with discounts agreed in patient access schemes. Cytotoxic chemotherapy with dacarbazine can be considered for patients with stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable. Further chemotherapy should not be routinely offered to patients with stage IV metastatic melanoma who have been previously treated with dacarbazine, except in the context of a clinical trial. This guideline predates the availability of trametinib, pembrolizumab and nivolumab.

The European Society for Medical Oncology (ESMO) published an update to their cutaneous melanoma clinical practice guidelines in September 2015.[11] This made recommendations on first and second line treatment options for metastatic disease (Stage IV) with anti-PD1 antibodies (pembrolizumab, nivolumab), ipilimumab, an anti-CTLA4 antibody, for all patients, and BRAF inhibitors (vemurafenib, encorafenib and dabrafenib) in combination with MEK inhibitors (binimetinib, cobimetinib and trametinib) for patients with BRAF-mutant melanoma. BRAFi/MEKi combination

therapy is noted to have a high chance of rapid response and improved quality of life outcomes in patients with bulky, symptomatic metastasis BRAF-V600 mutated melanoma. Cytotoxic drugs such as dacarbazine, temozolomide, taxanes, fotemustine, platin derivatives or others, cytokines (IFNs, interleukin-2) or combinations may considered if access to new treatment compounds is not available.

A collaboration of multi-disciplinary experts from the European Dermatology Forum, the European Association of Dermato-Oncology and the European Organization of Research and Treatment of Cancer published; Diagnosis and treatment of melanoma, European consensus-based interdisciplinary guideline - update 2012. [12] It states that the two main goals of systemic therapy of metastatic disease are prolongation of survival and reduction of tumour size or load with a resultant increase in symptom-free course or a decrease in symptoms. Treatments included in the guidance are targeted therapy (vemurafenib), immunotherapy (ipilimumab) and chemotherapy (dacarbazine). The guidance notes there are insufficient data to establish a treatment algorithm for stage IV melanoma. However general principles include:

- BRAF mutated patients should be offered treatment with BRAF inhibitors or experimental drugs blocking the MAP kinase and PI3K pathways, preferably still in the context of clinical trials designed to reduce the emergence of drug resistance.
- Patients whose disease progresses on first-line treatment and with health status of presumably six or more months should be offered ipilimumab or other immunotherapies in the context of clinical trials as they are made available.
- Non-BRAF-mutated patients and those progressive under BRAF inhibitors and immunotherapies should be considered for chemotherapy.

This guideline predates the availability of trametinib, dabrafenib, pembrolizumab and nivolumab.

The British Association of Dermatology issued revised UK consensus guidelines for the management of cutaneous melanoma in 2010.[13] This guideline predates the availability of newer agents.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 72; Cutaneous Melanoma in July 2003 (and updated in February 2004).[14] This guideline predates the availability of biological therapies but an update is in progress and is expected in summer 2016.

Additional information: comparators

For the treatment of patients with advanced melanoma with BRAF V600 mutations, the most relevant comparators are BRAF inhibitors (dabrafenib and vemurafenib).

Cost of relevant comparators

Drug	Dose Regimen	Cost per 28 days (£)
Trametinib plus dabrafenib	**2mg orally once daily plus 150mg orally twice daily continuously**	**10,080**
Vemurafenib	960mg orally twice daily continuously	7,000
Dabrafenib	150mg orally twice daily continuously	5,600

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4 April 2016. Costs do not take any patient access schemes into consideration. During COMBI-d, the median duration of treatment was 11.0 months for trametinib plus dabrafenib (£110,880) and 8.0 months for dabrafenib (£44,800). During COMBI-v, the median duration of treatment was 10.0 months for trametinib plus dabrafenib (£100,800) and 6.0 months for vemurafenib (£42,000).

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This assessment is based on data submitted by the applicant company up to and including 13 May 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.