# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final appraisal document

# Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma

## 1 Recommendations

1.1 Dabrafenib with trametinib is recommended, within its marketing authorisation, as an option for the adjuvant treatment of resected stage III BRAF V600 mutation-positive melanoma in adults. It is recommended only if the company provides dabrafenib and trametinib with the discounts agreed in the commercial arrangements.

### Why the committee made these recommendations

There are currently no adjuvant treatments available for stage III BRAF V600 mutation-positive melanoma and there is a substantial risk of the cancer returning and becoming incurable. Dabrafenib with trametinib is a new adjuvant treatment aimed at curing the cancer by reducing the likelihood that it will spread. It is therefore an important development in managing stage III melanoma.

Clinical trial evidence shows that dabrafenib with trametinib extends the length of time people have before their melanoma recurs compared with routine surveillance. Evidence from the trial and from clinical experts strongly suggests that it also increases the overall length of time people live by reducing how many people develop metastatic disease.

Cost-effectiveness estimates for dabrafenib with trametinib are in the range usually considered a cost-effective use of NHS resources. Therefore it can be recommended.



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# 2 Information about dabrafenib with trametinib

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| **Anticipated marketing** | On 26 July 2018 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending a variation to the terms of the marketing authorisations for the medicinal products dabrafenib and trametinib. The new indications are as follows:<br>• Dabrafenib, in combination with trametinib, is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.<br>• Trametinib, in combination with dabrafenib, is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection. |
| **Dosage in the marketing authorisation** | For dabrafenib, the recommended dose is 150 mg taken orally, twice daily. For trametinib, the recommended dose is 2 mg taken orally, once daily. |
| **Price** | The list price for 28 capsules of dabrafenib 75 mg is £1,400 and 30 tablets of trametinib 2 mg is £4,800 (company submission).<br>The company has a commercial arrangement for each drug. This makes dabrafenib with trametinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount. |

# 3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Novartis and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

## *Clinical need and current management*

### People with completely resected stage III BRAF V600 mutation-positive melanoma have a high unmet clinical need

3.1 Melanoma is more common in younger people than other cancers. It has a substantial effect on patients, carers and wider society. Around half of people with stage III melanoma will experience a distant (metastatic) recurrence, for which the 5 year survival prognosis is poor (ranging from

5% to 20%). Advanced melanoma can cause severe and debilitating symptoms and is life threatening. Standard treatment for stage III melanoma is resection of the tumour and associated lymph nodes but people are still at high risk of disease recurrence, with 5- and 10-year relapse-free survival rates of 57% and 36%. The clinical and patient experts explained that there is a need for earlier active treatment after resection to prevent both recurrence at the original site and the development of metastatic disease. The committee concluded that people with resected stage III BRAF V600 mutation-positive melanoma have a high unmet clinical need and would value new treatment options.

**Adjuvant treatment aims to cure the disease and is an important development in the management of stage III melanoma**

3.2 Standard of care for people with resected stage III BRAF V600 mutation-positive melanoma is routine surveillance. This includes regular clinical review and imaging surveillance. Adjuvant radiotherapy and immunotherapy after tumour removal are not widely used in UK practice. The clinical experts explained that the aim of adjuvant treatment is to remove any residual microscopic disease after resection. This reduces the risk of relapse and progression to metastatic disease. They further explained that the biology of the disease means that relapse usually happens in the first few years after resection, but this had not been seen with dabrafenib with trametinib in the clinical trial. Their expectation is that a substantial number of people will be cured by having a course of dabrafenib with trametinib after surgical resection. The committee noted that the ERG's clinical experts suggested that adjuvant treatment may only delay disease recurrence, rather than prevent it. However, the Cancer Drugs Fund clinical lead explained that dabrafenib with trametinib taken for advanced disease is not considered curative. But, there are precedents from other malignancies in which non-curative systemic therapy for advanced disease does increase the cure rate if given at an early stage of disease post-surgery, for example breast cancer, colorectal cancer and non-small cell lung cancer. He therefore considered it unlikely

that adjuvant treatment with dabrafenib with trametinib would have no long-term survival benefit in melanoma. The committee concluded that adjuvant treatment with dabrafenib with trametinib for resected stage III BRAF V600 mutation-positive melanoma is a potentially innovative therapy. It aims to reduce the risk of relapse and death and is therefore an important development in the management of melanoma.

## *Clinical evidence*

### The clinical evidence is representative of clinical practice in England

3.3 The clinical evidence came from COMBI-AD, which was a double-blind randomised placebo-controlled trial. COMBI-AD assessed the clinical effectiveness of dabrafenib with trametinib in people with resected stage III BRAF V600 mutation-positive melanoma. The ERG explained that there were some limitations of the trial, but that overall it was well conducted and the baseline demographic characteristics of patients were comparable to patients in the UK. The committee understood that the American Joint Committee on Cancer (8th edition) had redefined stage III melanoma groupings and included an additional stage IIID subgroup. The committee considered whether this would affect the generalisability of COMBI-AD (which used staging based on the 7$^{th}$ edition) to clinical practice in England in the future. The clinical experts explained that the new IIID subgroup is a subset of the IIIC subgroup and therefore these patients were included in the trial. The committee concluded that COMBI-AD was well conducted and representative of clinical practice in England.

### Dabrafenib with trametinib increases relapse-free survival

3.4 Investigator assessed relapse-free survival was the primary end point in COMBI-AD. At a median follow-up of 2.8 years, median relapse-free survival in the dabrafenib with trametinib arm had not yet been reached because of the low event rate. Relapse-free survival was substantially longer in the dabrafenib with trametinib arm than in the placebo arm, representing a 53% lower risk of relapse or death (hazard ratio [HR] 0.47,

95% confidence interval [CI] 0.39 to 0.58; p<0.001). The Kaplan–Meier plot showed that relapse-free survival was higher for the treatment arm compared with placebo at all time points, suggesting an early and sustained advantage. The clinical experts explained that they expected to see continued separation of the curves with maturing data, to reflect the biology of the disease (in which the risk of relapse decreases substantially a few years after treatment). The committee concluded that dabrafenib with trametinib increases relapse-free survival compared with placebo.

**Dabrafenib with trametinib is expected to increase overall survival**

3.5 Median overall survival was not reached in either arm of the trial, suggesting that more than 50% of patients were still alive at the time of data cut-off. However, the hazard ratio for death was 0.57 (95% CI 0.42 to 0.79; p=0.0006) for dabrafenib with trametinib compared with placebo. The committee considered that the results, although immature, were extremely promising and, together with the evidence from the clinical experts (see section 3.2), strongly suggest that combination adjuvant treatment with dabrafenib with trametinib will increase overall survival.

## *Adverse events*

**Dabrafenib and trametinib have manageable adverse event profiles**

3.6 The most frequently reported adverse events in the treatment arm were pyrexia (63% of patients), fatigue (47%), and nausea (40%). Serious adverse events happened in 36% of patients and 26% of patients permanently stopped taking dabrafenib and trametinib because of adverse events. However, the clinical and patient experts explained that dabrafenib and trametinib are generally well-tolerated. They stated that side effects are manageable with quality of life maintained, and that treatment is well adhered to. The committee therefore concluded that dabrafenib and trametinib have manageable adverse event profiles.

## *The company's economic model*

### The model is appropriate for decision making

3.7 The company presented a 4 state-transition model comparing dabrafenib with trametinib with routine surveillance. The model was divided into 2 periods: the first 50 months, corresponding to the maximum follow-up in COMBI-AD, and the period beyond this to the end of the time horizon (50 years). Different curves were fitted to the 2 time periods and the distribution of events (loco-regional recurrence, distant recurrence and deaths) in each period also differed. The committee noted the comments from the ERG that the model structure was unusual because the cost-effectiveness estimates were not reliant on any modelled overall survival even though it was anticipated that this would differ between the arms. The committee considered that the company's approach was appropriate given the immaturity of the overall-survival data at the time of the modelling and that the model was suitable for decision making.

### The choice of curve for modelling relapse-free survival is the key driver in the economic analysis

3.8 A key uncertainty in the economic analysis was the choice of curves for modelling relapse-free survival, and the committee considered which curves were most appropriate. The company fitted different parametric functions to the trial data and considered the log-logistic unrestricted mixture model to provide the best visual and statistical fit to the relapse-free survival seen in the trial. The committee noted the ERG's comments that curve choice for extrapolation of relapse-free survival beyond the trial period is dependent on whether treatment with dabrafenib with trametinib is believed to cure disease or postpone recurrence. It recalled the views of the clinical experts that treatment is expected to cure some patients (see section 3.2). The clinical experts identified the company's log-logistic unrestricted mixture model followed by one of the alternative models presented by the ERG, the flexible parametric fit model, as the most clinically plausible because they showed continued separation of the

curves. The committee acknowledged that the choice of curve had a substantial effect on the cost-effectiveness estimates and accepted the clinical experts' first preference for the log-logistic unrestricted mixture model and then the flexible parametric fit model.

**Using data from the placebo arm of a trial of adjuvant immunotherapy to model long-term relapse-free survival is not adequately justified**

3.9 Beyond the first 50 months of the trial, the company extrapolated the results from COMBI-AD using the placebo arm of the international EORTC 18071 trial. This compared adjuvant ipilimumab with placebo in people with completely resected stage III melanoma. The ERG did not consider this approach appropriate because it locked in the proportionate survival gain at 50 months, with survival in the placebo arm being around 80% of survival in the treatment arm from month 50 onwards. Also, the ERG highlighted generalisability concerns about applying common risks from the placebo arm of a trial in a mixed BRAF population to the exclusively BRAF-positive population of COMBI-AD. The company had not explored other external sources such as AVAST-M (a UK trial of adjuvant bevacizumab), which may be more generalisable to clinical practice in England than the EORTC 18071 trial. The committee noted the ERG's comments that the company had rejected a number of parameterisations of the COMBI-AD relapse-free survival data because the dabrafenib with trametinib curves fell below the placebo curve. However, the ERG considered that this was minimal and did not happen until well into extrapolation, and therefore the company had not adequately justified why these curves should be rejected. The committee concluded that using data from the placebo arm of EORTC 18071 to model long-term relapse-free survival had not been adequately justified by the company.

**The ERG's and company base-case ICERS are very similar despite different methods of extrapolation, and fall in the range that can be considered cost effective**

3.10 The ERG made a number of changes to the company's base-case model such as revised assumptions for subsequent therapy and monitoring. The committee considered that these were appropriate but that the model was not sensitive to changes in these assumptions. The main driver of the cost-effectiveness modelling is the projection of long-term relapse-free survival. The ERG used parameterised curves derived from COMBI-AD for modelling relapse-free survival and the company used the placebo arm of EORTC 18071 for relapse-free survival after 50 months (see section 3.9). Using the ERG's base-case assumptions (alongside the committee's 2 preferred curves for modelling relapse-free survival, see section 3.8), the incremental cost-effectiveness ratios (ICERs) ranged from £20,701 per quality-adjusted life year (QALY) gained for the log-logistic unrestricted mixture model and £20,167 per QALY gained for the ERG's flexible parametric fit model. The committee noted that these were almost identical to the company's base-case ICER of £20,039 per QALY gained. The committee further noted that the results were consistent across the ERG's scenario analyses and were in the range normally considered cost effective. It therefore concluded that dabrafenib with trametinib is a potentially innovative treatment for stage III melanoma and represents a cost-effective use of NHS resources. Therefore, it can be recommended for routine commissioning.

# 4 Implementation

4.1 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.

4.2 The Welsh ministers have 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 2 months of the first publication of the final appraisal document.

4.3 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 resected stage III BRAF V600 mutation-positive melanoma and the doctor responsible for their care thinks that dabrafenib with trametinib is the right treatment, it should be available for use, in line with NICE's recommendations

# 5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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
July 2018

# 6 Appraisal committee members and NICE project team

## *Appraisal committee members*

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

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.

## *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.

**Sana Khan**
Technical Lead

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**Thomas Feist**
Project Manager

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