NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dabrafenib for treating unresectable, advanced or metastatic BRAFV600 mutation-positive melanoma [ID605]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Melanoma Focus

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

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What is the expected place of the technology in current practice?
How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The median survival of patients with metastatic melanoma is approximately 6 months. For many years, the cytotoxic agent dacarbazine was the mainstay of treatment for unresectable melanoma but the response rate is only 5-15% with no improvement in overall survival (OS).

Activating BRAF mutations are found in about half of patients with advanced melanoma. Vemurafenib, an inhibitor of mutant BRAF, was recommended by NICE in December 2012 for the treatment of locally advanced or metastatic BRAF V600 mutation-positive melanoma (NICE TA 269). Its use is also accepted by the Scottish Medicines Consortium. The update of the BRIM-3 trial of vemurafenib vs dacarbazine (McArthur et al, 2014) showed that the response rate to vemurafenib was 57%, median progression-free survival was 6.9 months, and median overall survival was 13.6 months. The most frequent toxicities were cutaneous squamous cell carcinomas, abnormal liver function tests, joint pain, rash, sun sensitivity, nausea and fatigue. Vemurafenib is currently the standard of care for patients with an activating BRAF mutation.

Dabrafenib (Tafinlar; GSK2118436) is an inhibitor of the BRAF V600 protein kinase. In May 2013, the FDA approved dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation. The EMA has also recommended dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

The BREAK-3 trial was a phase III open-label crossover study in 250 patients with BRAF V600E mutation-positive unresectable or metastatic melanoma who had not received previous antitumour therapy, apart from interleukin-2 in the metastatic setting. Patients were randomised 3:1 to dabrafenib 150mg bd (n=187) or dacarbazine (n=63). The primary endpoint was progression free survival. On progression, patients in the dacarbazine arm could cross over to treatment with dabrafenib, which occurred in 56% of cases. PFS was 6.9 months in the dabrafenib arm compared to 2.7 months in the dacarbazine arm (HR 0.37, 95% CI 0.24-0.58; p<0.0001). The overall response rate was 52% for dabrafenib and 7% for dacarbazine. The median overall survival was 18.2 months for dabrafenib and 15.6 months for dacarbazine (HR 0.76, 95% CI 0.48-1.21). The most common adverse events with dabrafenib were hyperkeratosis (37%), headache (32%), fever (28%), joint pain (27%), skin papilloma (24%), alopecia (22%) and palmar-plantar erythrodysaesthesia syndrome (20%), photosensitivity (3%) and cutaneous squamous cell carcinoma (5%).

The BREAK-MB trial was an open-label study with dabrafenib for patients with BRAF-mutation positive melanoma who were not previously treated for brain

metastases (A. n=89) or who had progressed on local treatments (B. n=83). The primary endpoint was the proportion of patients who achieved an overall intracranial response and was 39.2% in cohort A and 30.8% in cohort B. Median PFS was 3.7/3.8 months and overall survival was 7.6/7.2 months. Treatment-related adverse events of grade 3 and above occurred in 22% of patients. 6% developed squamous cell carcinomas. The most frequent serious adverse events included pyrexia (6%), intracranial haemorrhage (6%; one treatment-related), & squamous-cell carcinoma (6%).

The results of the Combi-D study of dabrafenib with trametinib or placebo were presented at ASCO 2014. The response rate to dabrafenib monotherapy was 51%, and median progression-free survival was 8.8 months.

It is our recommendation that dabrafenib be made available as first line treatment for eligible patients with metastatic BRAF-mutation positive melanoma.We also recommend that dabrafenib be available for patients responding to, but intolerant of, vemurafenib beyond 2 months of initial treatment.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

This technology will only apply to patients with BRAF mutation positive tumours.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

This technology would be used in pre-existing specialist oncology clinics.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Dabrafenib is currently available through the Cancer Drugs Fund for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation and intolerance to vemurafenib where all of the following criteria are met:
1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Advanced melanoma
3. BRAF V600E mutation
4. PS 0 or 1
5. Severe intolerance necessitating discontinuation of vemurafenib within 2 months of initiating vemurafenib
6. An absence of disease progression whilst on full dose vemurafenib

7. No other previous systemic therapy for the treatment of melanoma other than vemurafenib

As it must be applied for on an individual basis, it should be being used within its licensed indications.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are no published UK guidelines for the use of dabrafenib for metastatic melanoma, as this is a new technology. The evolution of treatment algorithms comes from clinical trials that use dabrafenib as a single agent or in combination.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The clinical trials reflect clinical practice to a large extent, and this can be extrapolated to a UK setting. Dabrafenib has not been studied in patients whose performance status was 2 or worse, or in patients with moderate renal or liver impairment. Such patients were studied in the vemurafenib safety study (Larkin et al, 2014) and vemurafenib was active in these patients, with no unexpected toxicities, although progression-free survival was shorter than in patients whose PS was 0-1. PFS was measured in the BREAK-3 trial and is a good surrogate of outcome that allows for crossover.

It is likely that dabrafenib will be better tolerated than vemurafenib, as it causes no significant photosensitivity, and appears to cause less arthralgia and second skin tumours. Monotherapy with BRAF inhibitors may be superceded by combination treatment in the next few years, but combinations will not be suitable for everyone

(e.g. for patients with refractory hypertension, heart failure, or certain eye conditions), and dabrafenib would continue to be useful for these patients.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Vemurafenib and dabrafenib have not been directly compared. It is possible that the results of the Combi-D and Combi-V trials which share an arm (the combination of dabrafenib and trametinib) will permit an indirect comparison. However, we can compare the adverse events reported in the BREAK-3 trial with dabrafenib and in the BRIM-3 study of vemurafenib.
Side-effects grade 2 and above:
Hyperkeratosis 14% v 6%
Arthralgia 6% v 21%
Squamous cell carcinomas 5% v 12%
Photosensitivity 0% vs around 40%
The vemurafenib safety study found similar results, including 31% photosensitivity and 39% arthralgia.

There are not yet any adverse events that were not apparent in clinical trials but have come to light subsequently during routine clinical practice.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The first results of the Combi-V trial of dabrafenib and trametinib vs vemurafenib are awaited. The BREAK-1 and BREAK-2 trials were updated at ASCO 2014, but have not yet been published.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

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Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The use of dabrafenib could be easily accommodated. NHS staff would not need extra education and training.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No adverse impact identified.