

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Vemurafenib for the treatment of unresectable locally advanced or metastatic BRAFV600 mutation-positive malignant melanoma

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: Drs Jenny Hughes and Stephen Keohane

Name of your organisation: British Association of Dermatologists (Therapy & Guidelines sub-committee and Skin Cancer sub-committee)

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- 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?

→The standard treatment is with single-agent dacarbazine.

Is there significant geographical variation in current practice?

→Dacarbazine is available throughout the UK.

→There are, however, only certain units throughout the UK that are currently taking part in clinical trials involving vemurafenib.

Are there differences of opinion between professionals as to what current practice should be?

→No, but there are many more agents soon to be licensed including vemurafenib and so practice may end up being different between different professionals.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

→Dacarbazine is the standard of care and has a response rate of about 12%.

→Other treatments include temozolomide, cisplatin, taxols, immunotherapy and vaccines; none have been shown to be better than standard of care except ipilimumab (immunotherapy), which has recently been licensed for treatment of melanoma and has about a 25-30% response rate.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

→Yes, those patients with ocular and mucosal melanomas.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

→No.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

→Secondary care.

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Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

→ Clinical nurse specialists in melanoma will be required but most units that will be treating patients with melanoma should have these CNSs in place as a requirement of improving outcomes guidance for skin cancer and peer review.

If the technology is already available, is there variation in how it is being used in the NHS?

→ The technology is only available as part of a clinical trial at present. Once licensed, the treatment regimes will be the same.

Is it always used within its licensed indications?

→ Yes.

If not, under what circumstances does this occur?

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.

→ Presently there are only guidelines for treatment regime and monitoring that have been produced by Roche pharmaceuticals as part of the ongoing clinical trials.

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?

→ The treatment is given in tablet form twice daily and therefore easy to take.

→ The patient is not required to be in hospital for the treatment.

→ The alternative dacarbazine is given as an infusion.

→ Regular blood monitoring is required.

→ No concomitant medication is needed. This is a real advantage of the medication.

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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.

- The technology will only be available to 40% of melanoma patients with stage IV disease who prove to be BRAF mutation positive.
- Treatment may be interrupted for grade 3 side effects (mostly rash or joint pains).
- Drug is then often re-started at a lower dose.
- CT scans will be required every 4-6 weeks to assess response.

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.

- Yes it will do.

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?

- Once the drug is licensed then the drug will be available throughout secondary care oncology units that treat patients with melanoma.

What, in your view, are the most important outcomes, and were they measured in the trials?

- Response rates of 50% and overall survival. Both measured in clinical trials published in the NEMJ: 1 and 2 below

1. Chapman PB, Hauschild A, Robert C *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *New England Journal of Medicine* 2011; **364**:2507-2516.
2. Flaherty *et al.* Inhibition of mutated, activated BRAF in metastatic malignant melanoma, *New England Journal of Medicine* 2010; **363**:809-819.

If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

- N/A.

What is the relative significance of any side effects or adverse reactions?

- Significant side effects include skin toxicity with grade 2 and 3 rash reported in 20%.
- Squamous cell carcinomas also arise in about 20% of patients.
- Photosensitivity is also a problem.

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In what ways do these affect the management of the condition and the patient's quality of life?

- Most skin side effects can be managed with topical emollients and steroids.
- Grade 3 eruptions can be managed with dose interruption and restarting at a lower dose.
- Joint pain again may require dose interruption and systemic steroids.
- As the treatment is long-term in some patients, side effects do need to be managed appropriately to minimise effect on 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?

- N/A – not in routine clinical practice yet.

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?

- No. Dr Louise Fearfield (BRIM3 trial) is currently writing an observational study detailing more clearly the skin toxicity, which includes a management algorithm. She would be happy to provide this document if asked, which is due to be submitted to the British Journal of Dermatology in the next few weeks.

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.

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.

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

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How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?

→ Give patients a potential treatment that has benefits.

Would NHS staff need extra education and training?

→ Need to be aware of treatment regimes and possible toxicities but no specific training would be needed prior to treatment.

Would any additional resources be required (for example, facilities or equipment)?

→ No.

Equality

Are there any issues that require special attention in light of NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others?

→ No