Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Trametinib in combination with dabrafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma

Thank you for agreeing to make a submission 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 submission, 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:

Name of your organisation: British Association of Dermatologists
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)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?
Patients with a BRAF mutation are treated with ipilimumab (first- or second-line), single agent BRAF inhibitors (either dabrafenib or vemurafenib) (first- or second-line), and pembrolizumab (third-line).

Is there significant geographical variation in current practice?
Some centres will be more involved in clinical trials than others so variation will depend on this.

Are there differences of opinion between professionals as to what current practice should be? **Although there are no published guidelines, the sequencing of treatments can vary between centres, but otherwise the treatment is the same.**

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
The alternatives, vemurafenib and cobimetinib, have only been available as part of clinical trials. (Larkin et al. *N Engl J Med* 2014; 371:1867-1876.) The combined treatment was noted to have a non-significant increase in toxicity.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
Those with high LDH level and brain metastases at presentation generally have a worse prognosis.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
Only those with a BRAF mutation can receive this treatment.

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

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
Specialist nursing and support from other specialities: dermatology, ophthalmology, gynaecology.

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?
It is not available as a combined treatment.

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.

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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 major trial by Robert et al. (*N Engl J Med* 2015; 372:30-39) is relevant to this combination treatment, showing increased overall survival compared to vemurafenib alone with no increase in toxicity. It is an oral medication, therefore easy for the patients to take and can be monitored on an outpatient basis.

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.
This combination treatment is suited for first-line treatment, to be given to patients with more rapidly progressive disease where ipilimumab would not work quickly enough. At the moment, anti-PD1 agents are not available as first-line treatments. Stopping will be governed by progression as determined by RECIST or by toxicity.

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.

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?
They reflect current practice.

What, in your view, are the most important outcomes, and were they measured in the trials?
PFS, OS and ORR were measured in the Robert study. This was only up to 12 months, so long-term data is not available.

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

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?
Of note, the incidence of development of cutaneous squamous cell carcinoma was much lower in the combination group than the vemurafenib group (1% vs. 18%, respectively). This is due to the MEK inhibitor helping to inhibit the paradoxical activation of the MAPK pathway that occurs with single-agent BRAF inhibitors.
This is very beneficial to the patient, who will tolerate the treatment better; with this reduction in toxicity, including overall skin toxicity rates (rash, benign skin tumours,

etc.), they will be managed much better. There would be less need for intervention from other specialities as well.

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.

Implementation issues

The NHS is required by the Department of Health 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 to vary this direction.

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)?

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.