Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dabrafenib for the treatment of unresectable, advanced or metastatic BRAFV600 mutation-positive 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: [redacted] **submitting comments on behalf of the :**

Name of your organisation: NCRI/RCP/RCR/ACP/JCCO

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?

Patients with advanced melanoma routinely have their BRAF mutation status determined by genotyping of a previous tumour sample obtained at the time of diagnosis. Just under 50% tumours harbour a BRAFV600 mutation. The majority of these patients treated outside of a clinical trial will be offered vemurafenib as standard of care.

Since NICE guidance in December 2012, vemurafenib is available across England and Wales without restrictions.

Melanoma practice is currently evolving and the position of immunotherapy is particularly noteworthy. Ipilimumab was approved by NICE (December 2012) for the treatment of patients with advanced melanoma who have received prior systemic therapy, irrespective of BRAF mutation status. Currently, ipilimumab is therefore a '2nd line' treatment for BRAF mutant advanced melanoma patients. However, a first line license was obtained in Europe in November 2013 and NICE submission is pending. In addition, PD-1 inhibitors are being tested as first line treatment of advanced melanoma patients and early phase trial data have reported high rates of durable responses. Thus, immunotherapy is likely to be increasingly used a first line treatment option for BRAF mutant advanced melanoma, with BRAF targeted agents being used subsequently.

Conventional cytotoxic chemotherapy is now largely relegated to consideration after BRAF targeted agents (BRAFi) and immunotherapy in these patients.

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?

While V600E is the most common BRAF mutation, other V600 mutations - K, D, R - have all been identified. It is clear that patients with BRAFV600K mutant melanoma also benefit from BRAFi.

BRAFi has activity in patients with brain metastases.

The sequencing of BRAFi and immunotherapy may be impacted by patient characteristics such as perfomance status (PS), burden of disease and rate of disease progression. In contrast to ipilimumab which is more likely to benefit good PS patients with life expectancy of 12 weeks or more, BRAFi can salvage patients with poor PS, high volume disease which is rapidly progressing. However, resistance to BRAFi is inevitable and some patients progress too rapidly to benefit from

immunotherapy. Hence, this is justification to consider immunotherapy as a first line option.

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)?

These biological agents should be prescribed by specialist melanoma oncologists based in secondary care. Patients should be managed in specialist melanoma oncology clinics and have access to specialist nurses trained in managing drug-related side effects.

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 has been accessed in clinical trials conducted in specialist NHS centres over the last 2-3 years. It is currently available in England via the CDF within the licensed indication as well as additional specific criteria, for patients who are intolerant of vemurafenib.

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.

These agents are not part of any specific UK clinical guidelines currently.

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?

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?

The BREAK3 trial was conducted outside of the UK and convincingly shows that dabrafenib is as active as vemurafenib, in terms of response rate and PFS/OS hazard ratios compared with the standard arm, dacarbazine. It is noteworthy that the control dacarbazine arm is rather atypical in having a higher PFS than anticipated, but the HRs are comparable to the BRIM3 vemurafenib data.
The side effect profile of dabrafenib is slightly different to vemurafenib. Photosensitivity rarely occurs with dabrafenib, although pyrexia is more frequent. Both drugs generate skin lesions, which may vary from benign papillomas, to keratoacanthomas and SCCs.

The BREAK MB phase II trial confirmed that dabrafenib has activity in patients with brain metastases.

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 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)?

Specialist nurse and acute oncology team education regarding management of drug-related toxicities. In particular, pyrexia associated with dabrafenib not normally a sign of infection and myelosuppression is extremely rare, so there needs to be an understanding that these patients are not at very low risk of neutropaenic sepsis.

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 issues