Appendix G -Professional organisation statement template

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:

Dr Patrick Cadigan, RCP registrar submitting comments on behalf of :

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

Comments coordinated by Professor Martin Gore, Royal Marsden Hospital NHS Foundation Trust

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)?

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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?

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?

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)?

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?

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.

Metastatic/locally advanced unresectable melanoma has an extremely poor prognosis with a median survival of 6-9 months 5 year survival of about 10%. Clinical trial entry is regarded as a standard of care for any patient with advanced/metastatic melanoma. Locally advanced/metastatic BRAF V600 mutation-positive melanoma is currently treated in fit individuals in the 1st line setting outside the context of a clinical trial with dacarbazine (DTIC), an agent associated with a response rate of approximately 5-10%, a median progression-free survival of approximately 6 weeks and a median overall survival of approximately 8 months. In the 2nd line setting, standard therapy is the anti-CTLA4 antibody ipilimumab at 3mg/kg. This agent is associated with an approximate chance of 15% of prolonged (i.e. measured in years) disease control. Ipilimumab is currently generally available in England via the Cancer Drugs Fund. There is no significant difference in opinion between professionals or geographical variation in clinical practice in advanced/metastatic melanoma. The major disadvantage of DTIC is that it has very limited efficacy. In a 1st line phase III trial versus DTIC (BRIM-3, Chapman et al NEJM 2011; 364: 2507-16) in which the UK was a major recruiter, vemurafenib was associated with a response rate of approximately 50%, a median progression-free survival of between 5 and 6 months (p<0.0001, HR=0.26) and a median overall survival in excess of 12 months (p<0.0001, HR=0.37). Importantly, in patients with a significant symptom burden, vemurafenib often causes an improvement in symptoms within days or weeks.1

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Vemurafenib, when licensed in the EU, will replace DTIC as standard therapy for locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. This has already happened in the US after the licensing of the drug in August 2011. Vemurafenib will be prescribed by oncologists in specialist clinics. Vemurafenib is administered orally and so less use will be made of day unit resources as DTIC is given intravenously. Currently vemurafenib is only available in the UK as part of a large phase II 'safety study' which is a means for patients to access the drug prior to licensing. The development of vemurafenib has been too recent for incorporation into any guidelines. Currently no information is available which predicts which patients with V600 BRAF mutant melanoma may gain greatest benefit from vemurafenib therapy.

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?

In general, vemurafenib is easier to use than DTIC as it is given orally rather than intravenously. Prophylactic anti-emetics are given with DTIC but not vemurafenib so this is a further convenience. The timing of initiation of vemurafenib therapy is likely to be no different from the timing of initiation of DTIC therapy and this represents a judgement on the part of the treating clinician in discussion with the patient. A difference between DTIC and vemurafenib is that vemurafenib is targeted to melanomas driven by BRAF V600 mutations (approximately 50% of cutaneous melanomas) so tumours are

screened for BRAF V600 mutations to determine eligibility and potential benefit from vemurafenib. The technology used to screen for BRAF mutations is similar to that used to screen for EGFR mutations in non-small cell lung carcinoma, KIT in gastrointestinal stromal tumours and KRAS in colorectal cancer. There is no molecular marker to select patients that will benefit from ipilimumab therapy; the fact that patients can be selected for vemurafenib therapy by BRAF mutational analysis has benefits in terms of maximising efficacy, reducing toxicity and costs.

The trial population in the BRIM-3 trial is representative of UK clinical practice and the UK was a major recruiter to the trial. The most important outcome measures in the trial were progression-free and overall survival, both of which were significantly prolonged with vemurafenib in comparison with DTIC. Vemurafenib is associated with mild to moderate often cutaneous side effects. These side effects are usually manageable and fewer than 10% of patients stop treatment as a consequence of toxicity. Patients with symptoms from melanoma almost always have significant symptom control with vemurafenib and as such most patients feel much better after starting therapy than before.

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.

No information beyond the Phase I (BRIM-1), Phase II (BRIM-2) and Phase III (BRIM-3) trials.

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? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No extra training or additional resources would be required.

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.