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: [redacted] **submitting on behalf of:**

Name of your organisation: NCRI-RCP-ACP
Are you (tick all that apply):

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? 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, inoperable melanoma are normally genotyped for BRAF gene mutation status. Around 45% of melanomas harbour a BRAF mutation and patients with advanced BRAF mutant melanoma are eligible for BRAF inhibitor treatment as first line therapy (NICE TA 269, TA 321). However, probably around 2/3 of these patients are now being diagnosed early, with low volume, slowly progressing disease and these patients who are otherwise fit and well are more likely to be offered immunotherapy with either Ipilimumab or pembrolizumab initially, according to NICE guidance (TA 319, TA 268, TA 357). Those remaining patients with poorer prognosis advanced melanoma and shorter life expectancy characterized by features including high volume disease, high serum LDH, rapid disease progression, poor performance status and multiple brain metastases, or those progressing after immunotherapy, will be offered BRAF inhibitors.

BRAF inhibitors as single agents have response rates of approximately 50% and moderate toxicity, and are associated with a median progression free survival of around 7 months. Ipilimumab has low response rate (15-20%) but for those who benefit there can be durable response lasting some years, which translates to an overall survival advantage in comparison with cytotoxic chemotherapy in phase 3 trials. Toxicity is problematic, with 1in 10 patients being hospitalised for serious immune-related adverse events, although treatment is manageable in experienced hands. Pembrolizumab has a response rate of 30-40%, superior progression free and overall survival and lower severity of toxicity compared with ipilimumab in a phase 3 trial.

Vemurafenib was the first BRAF inhibitor made available for BRAF mutant metastatic melanoma patients. Dabrafenib became available later, but is gradually replacing vemurafenib as the BRAF inhibitor of choice, due to better side effect profile, while they are cost equivalent. Photosensitivity and other skin toxicities are a problem with vemurafenib, but photosensitivity is virtually non-existent with dabrafenib and other skin toxicities occur with lower severity and frequency.

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?

BRAF mutant melanoma represents around 45% of all melanomas.

There is a subgroup of poorer prognosis advanced melanoma patients with particularly short life expectancy untreated in the order of 3 -6 months median, characterized by features including high volume disease, high serum LDH, rapid

disease progression, poor performance status and multiple brain metastases. These patients are not good candidates for immunotherapy, but if their tumour harbours a BRAF mutation, treatment with BRAF targeted agents may help to control disease at least in the short term, with in some cases rapid improvement in unpleasant disease-related symptoms and improvement in quality of life. This subgroup in particular stands to gain from the new technology by maximizing their response rate and duration of benefit from treatment.

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?

Trametinib+Dabrafenib should be prescribed only by specialist melanoma oncologists in secondary care. It would always be used within licensed indication.

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.

NICE guidelines for melanoma management were published in July 2015 but do not cover this technology.

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?

Uniquely, the combination of trametinib+dabrafenib appears to generate less toxicity when compared with dabrafenib or vemurafenib monotherapy. In particular, skin toxicities are less frequent and severe. The main additional toxicity is that of pyrexia and chills. These are relatively minor and can be managed with good patient and healthcare professional education. These symptoms are rarely associated with infection or neutropaenia and only rarely result in hospital admission.

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.

Patients will discontinue upon radiological disease progression. Repeat imaging will therefore be necessary throughout the duration of treatment, at clinically appropriate intervals.

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?

Dabrafenib + Trametinib has been directly compared with dabrafenib in the Combi-D trial and with vemurafenib in the Combi-V trial. Both international multicentre clinical trials involved many UK centres so a high number of UK patients took part and have been treated with this combination regimen. The results of these 2 trials can be extrapolated to a UK setting.
Both trials have convincingly shown an improvement in all key end points of overall survival, progression-free survival, response rate and toxicity with the combination regimen compared with BRAF inhibitor monotherapy.

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?

As already described, the combination regimen appears to in fact be better tolerated than the single agent.

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.

N/A

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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)?

No significant changes of note in terms of treatment delivery.

The only significant costs will be in pharmacies given that patients remain on combination treatment longer than single agent BRAF inhibitor treatment because of increased duration of benefit.

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;

No

- 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;

No

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

No

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Please tell us what evidence should be obtained to enable the Committee to identify and consider such impact N/A