NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ipilimumab for previously untreated unresectable 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: [redacted]

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

Comments coordinated by: [redacted]

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)

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?

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Patients with advanced, inoperable melanoma are currently genotyped for BRAF gene mutation status. Most patients with BRAF mutant positive disease are offered treatment with BRAF directed therapy first line. This may be standard vemurafenib or alternative agents being tested in clinical trials.

BRAF wild type patients are currently offered cytotoxic chemotherapy or an alternative experimental therapy in a clinical trial as first line therapy.

Ipilimumab is offered as a second line option to both BRAF mutant and wild type patients.

Across England and Wales, there is little geographical variation in current practice following NICE approval of vemurafenib (TA 269) and ipilimumab (TA 268). There is little difference in opinion between professionals regarding current practice.

The new technology would place ipilimumab as a first line treatment option for both BRAF WT and mutant advanced, inoperable melanoma. In BRAF mutant disease, most patients are likely to still receive vemurafenib (or equivalent) as first line, since the majority of patients with this type of advanced melanoma have rapidly growing disease likely to need a rapid, early response to treatment which is offered by BRAF inhibitors. A lower % of these patients present with very low volume and/or slowly progressing disease, in whom ipilimumab is likely to be the preferred first line option over BRAF directed therapy, since these are the characteristics of patients more likely to benefit from immunotherapy.

In BRAF WT disease, ipilimumab would be appropriate for good ECOG PS (0-1) patients who are not rapidly progressing. ECOG PS 2 patients and those with rapidly progressing disease might be offered cytotoxic chemotherapy or experimental treatment within clinical trials in preference to ipilimumab, since they are less likely to cope with the potential side effects of ipilimumab and have the opportunity to benefit from immunotherapy, due to shorter life expectancy.

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?

As described above, BRAF genotype, ECOG PS, volume and rate of growth of disease will influence patient selection. There is no identified biomarker for sub groups of melanoma patients most likely to benefit. The above factors influence patients most likely to be put at risk from ipilimumab and will inform physician's decisions on whether to recommend treatment to a patient.

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)?

Ipilimumab should be used only by specialist melanoma oncologists in secondary care. There are no other routine requirements for additional professional input over and above what is already available to this group of patients. Around 1 in 10 patients may experience severe immune related toxicities and additional support from relevant specialists may be required to manage these, as well as access to the local acute oncology service.

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?

The technology is available and used in its current licensed indication in patients with advance melanoma who have received prior systemic therapy

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.

The national melanoma guidelines were published in 2010 and predate licensing of ipilimumab and vemurafenib. The only formal guidelines in use in the UK are the NICE TAs for these agents.

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?

Specialist melanoma oncologists are already familiar with use of ipilimumab. The dose and schedule in first line may be different, if the registration clinical trial forms the basis of licensing and NICE approval.
Baseline thyroid function tests are recommended.

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.

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Starting rules: patients should be ECOG PS 0-1 and not be rapidly progressing.

Patients with brain metastases should not be excluded.
Although response rates are lower in rarer forms of melanoma, its use should not be confined to cutaneous forms of melanoma onlyas patients with other forms have been shown to benefit

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?

The registration trial compared ipilimumab + dacarbazine to dacarbazine alone. Since dacarbazine chemotherapy is a first line standard of care for melanoma, the trial is relevant to UK practice. In reality, it is anticipated that dacarbazine contributed little to the trial outcome, so there is an expectation to use ipilimumab monotherapy first line, not in combination with dacarbazine.

The trial primary end point was overall survival, which is the most important outcome in this disease.

UK specialists recently undertook an analysis of real life use of ipilimumab in its current licensed indication, involving nearly 200 patients. In this retrospective review, patient outcomes were less good overall compared with the 2nd line trial data. However, if the analysis was confined to those patients who met the trial entry criteria (ECOG PS 0-1), outcomes were very similar.

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?

Ipilimumab has associated immune related side effects which can be severe and potentially life threatening in around 10% patients. Local practice suggests 1 in 10 patients may warrant hospitalisation.
These side effects were identified in clinical trials, which led to detailed algorithms being formulated to manage toxicity promptly and aggressively. Thus, while several patient deaths were recorded in the trials, in routine clinical practice, deaths due to ipilimumab have occurred extremely rarely.

Any additional sources of evidence

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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.

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)?

Implementation of ipilimumab as a first line therapy would not have any significant impact on delivery of care for this group of patients. NHS staff are already trained and resourced to use this treatment

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.

This technology should not impact on equality issues