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: 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)

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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.

Ipilimumab is a human monoclonal antibody that activates the immune system to fight melanoma by targeting a protein called Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4). Expression of CTLA-4 by Helper T cells inhibits recognition and destruction of cancer cells, but ipilimumab turns off the inhibitory mechanism, enabling immune-mediated killing of the cancer cells. Randomised clinical trials have established a survival benefit for melanoma patients treated with this drug and this was the first drug ever reported to produce a survival benefit (1).

Some patients treated with the drug survive for long periods, and four-year survival rates reported in pooled data from three phase 2 clinical trials were between 13.8 and 28.4% depending on dose. Treatment-naive patients treated at 10 mg/kg had a 4-year survival rate of 37.7% (95% CI 18.6-57.4) (2). This figure is very high compared with the average reported four-year survival for AJCC stage IV melanoma, which is around 15% (3). These data are very encouraging and the suggestion of a higher response rate for treatment-naïve patients suggests that first-line treatment may show increased response rates overall.

In a recent presentation at the ECCO meeting in Amsterdam October 2013, Prof Hodi and colleagues from Germany, France and the USA reported pooled data on 1861 patients treated with ipilimumab in 12 prospective studies, to provide a more precise estimate of ipilimumab's effect on long-term survival (Abstract number LBA 24). They reported that in 1861 patients treated in clinical trials, the median overall survival was 11.4 months. Among these patients, 254 patients (22%) were still alive after three years. There were no deaths among patients who survived beyond seven

years, at which time the overall survival rate was 17%. The longest overall survival follow-up in the database is 9.9 years. The authors also reported that the plateau in survival, started at three years and continued through to ten years.

These data therefore show:-

- That the four year survival for patients with stage IV melanoma treated with ipilimumab is somewhere around 22 to 28%;
- That four year survival figures might be better for treatment-naive patients;
- That there is a tail of people who appear to survive in the longer term, with a survival of 17% beyond seven years.

Ipilimumab therefore represents a major breakthrough in the treatment of melanoma, giving the potential for long-term survival for the first time. This was recognized by NICE in giving approval for second-line treatment of stage 4 melanoma.

Responses to ipilimumab however differ from that to chemotherapy, in that a proportion of responses are slow. It appears to take time for a response to be seen. Indeed, imaging early in treatment might appear to show progression before involution of the tumour. This phenomenon is thought to relate to short-term inflammation. In a phase III trial in which patients were randomized to ipilimumab, ipilimumab and a ganglioside vaccine, and vaccine alone (4), a small survival difference between the three arms was seen. Importantly for this discussion, of the 78 of the patients who received ipilimumab and survived 2 years or longer, 12 improved after 24 weeks on treatment. The authors therefore report that, in some patients, improvement in best response is late occurring after the induction period. It would appear, therefore, that some patients who survive in the long term therefore need time for their response to occur. The same study also reported that survival outcomes seemed to be higher in patients with less widespread disease (lower stage and lower LDH levels). The view of melanoma MDT teams is therefore that patients who have smaller volume disease may be more likely to respond and that earlier treatment would give them the time to respond. Hence there is a strong view that ipilimumab should be available for first-line treatment of stage 4 melanoma, especially for BRAF-negative patients unable to benefit from vemurafenib or other BRAF inhibitors.

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Aug 19;363(8):711-23. PubMed PMID: 20525992. Epub 2010/06/08. eng.
2. Wolchok JD, Weber JS, Maio M, Neyns B, Harmankaya K, Chin K, et al. Four-year survival rates for patients with metastatic melanoma who received ipilimumab in phase II clinical trials. Ann Oncol. 2013 Aug;24(8):2174-80. PubMed PMID: 23666915.
3. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009 Dec 20;27(36):6199-206. PubMed PMID: 19917835. Pubmed Central PMCID: 2793035. Epub 2009/11/18. eng.
4. McDermott D, Haanen J, Chen TT, Lorigan P, O'Day S, investigators MDX. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more

than 2 years following treatment in a phase III trial (MDX010-20). Ann Oncol. 2013 Oct;24(10):2694-8. PubMed PMID: 23942774.

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?

Please see above.

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.

Please see above.

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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)?

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.

N/A