

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Ipilimumab for the treatment of 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 Paul Lorigan

Name of your organisation



Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
Yes.
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
Yes.
- 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.)?
Yes. Senior Lecturer of the University of Manchester and Honorary Consultant in Medical Oncology at the Christie NHS Foundation Trust
- other? (please specify)
Chair, NCRI Melanoma Clinical Studies Group
Member of Executor of Melanoma Study Group

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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.

There are more than 2,000 new cases of metastatic malignant melanoma diagnosed in the UK every year. Until now, there have been no advances in the treatment of advanced melanoma for the last 30 years. Median survival for patients with advanced melanoma is less than 1 year and the majority of patients do not benefit from standard chemotherapy. The accepted standard treatment is single-agent dacarbazine with an expected response phase of less than 10%. The median progression-free survival with standard chemotherapy is only 6 weeks. In view of the poor outcome with standard chemotherapy, there is a consensus view internationally has been that standard of care for patients with advanced malignant melanoma is a clinical trial.

For the majority of patients treated with first-line chemotherapy who do not get a benefit, there is no accepted standard second-line treatment and the standard of care would be involvement in a clinical trial. For both the first- and second-line situations, a number of agents are used off licence, eg single-agent carboplatin, combination chemotherapy with carboplatin + paclitaxel, etc, but none of these treatments have been shown to confer a survival benefit. Many studies in the first- and second-line setting have looked at combination chemotherapy, biological agents (interleukin-2, interferon etc), combinations of biologicals, and combinations of chemotherapy and biological. Whilst response rates are higher with combination regimens, toxicity is also significantly greater and a number of meta-analyses have shown no survival benefit. Thus single-agent chemotherapy and clinical trial remain standards of care in the first-line setting and that clinical trial remains second-line therapy in the second-line setting.

A significant proportion of patients with advanced melanoma will go on to develop brain metastasis at some time. Brain metastases are very disabling, and treatment is largely ineffective. The prognosis for patients with brain metastasis is very poor and typically less than 3 months. This is a major area of treatment need.

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The incidents of melanoma increases with age but is disproportionately high in the younger age group, being the second most common cancer in the 16-35 year age group at present. The average lost of life is 20 years for a patient with advanced melanoma but clearly for the younger patients this is significantly greater.

Ipilimumab has shown a significant survival benefit in both the first- and second-line setting in clinical trials. I will confine my comments to the second-line setting as this is the current licence indication in Europe. However this drug is also licensed in the first-line setting in the US.

Ipilimumab has shown a median survival benefit of approximately 3 months for patients with advanced malignant melanoma treated in the second-line setting compared to a peptide vaccine. More importantly, there is evidence of long-term survival with an approximate doubling of expected survival from 1, 2 and 3 years.

Data from clinical trials indicates that ipilimumab is active in patients with brain metastasis. The majority of the data are for patients with asymptomatic brain metastases, and the magnitude of benefit is less than for visceral metastases

As yet, there are no identified factors that predict for a response to Ipilimumab.

Ipilimumab is associated with significant risk of toxicity. The treatment of advanced melanoma is a relatively specialist area given the relatively low number of patients. Patients should be managed as part of a skin specialist MDT (SSMDT) as defined by Improving Outcomes Guidance for malignant melanoma and skin cancers. Patients with advanced melanoma should only be treated in specialist centres.

Ipilimumab has just been licensed and is now available on the NHS in a number of regions and is being reviewed on a regional basis funded by Cancer Drugs Fund. One region has approved funding in the first-line setting. This reflects the licence indication in the US, evidence from a first-line study of similar benefit in the first-line setting or be it at a higher dose and with chemotherapy, and a general acceptance by clinicians that this drug is likely to be equally or more effective in the first-line setting and currently there is no useful alternate therapy. UK guidelines for management of malignant melanoma have been recently revised and published in 2010. However they pre-date the data from the first- and second-line trials of ipilimumab and the licensing of this drug.

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.

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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?

As set out earlier, this is the first treatment to show survival benefit in patients with metastatic malignant melanoma. The median survival benefit is approximately 3.5 months. There is an approximate doubling up of survival of 1, 2 and 3 years indicating that proportionate patients go on to be long-term survivors. Current standard of care in the second-line setting is a clinical trial. In view of this, routinely treating patients with ipilimumab will shift the treatment burden from the research side to the NHS side. It will also likely result in an increase in the number of patients receiving second line treatment. Comparative data from the UK, France and Italy have shown that the use of second line therapy in the UK is less than these countries, and the majority is given in the context of a clinical trial. This will change with the availability of a licensed treatment.

There are no significant extra tests over and above those routinely required for systemic therapy, ie routine blood, baseline and post-treatment imaging. In view of their mechanism of action - stimulating the immune system - patients with significant autoimmune disease or chronic infection would be excluded. Serology screens for hepatitis and HIV are routinely carried out.

Treatment is given as an intravenous infusion of approximately 90 minutes. There are no requirements for pre-medication.

Because of the mechanism of action, ie immune stimulation, assessment of response in the early stages is unreliable as tumour deposits may swell due to infiltration by inflammatory cells. This has now been well characterised and immune-related response criteria have been developed. However for a practical point of view, this means that the majority of patients will need to receive the full 4 cycles of treatment and there are no early indicators of either treatment response or failure.

Since publication of the data on the second-line study, there has been an expanded access programme in the UK. There has been significant uptake of this programme by the majority of melanoma specialists indicating that the licence indication reflects the clinical need and current UK practice.

There are data from the definitive second-line study that shows that quality of life is not significantly impacted on whilst patients are receiving treatment.

The toxicity profile of this drug reflects its mechanism of action. There is clear expectation that toxicity is less with increased experience. This is borne out by the fact that the toxicity in the recently published first line study was less of a problem, despite using a higher dose of treatment given with chemotherapy. Importantly,

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there were no treatment related deaths in this first lie study. This supports the assertion that treatment should only be given in specialist centres by experienced clinical teams.. A small number of patients that develop severe toxicity will require intensive management, perhaps in the context of a Critical Care Unit.

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.

Data on treatment patterns and outcomes in patients with advanced melanoma in the UK, France and Italy have been presented at the Perspectives in Melanoma meeting in 2010 and the NCRI National Cancer Conference in 2010. These data have been submitted for publication. A meta-analysis of second-line trial has been presented at ASCO 2011. Data on quality of life was presented at Perspectives of Melanoma meeting 2010.

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)?

Positive NICE guidance on this technology would require some NHS staff to undergo extra education and training. However this is likely to be taking place at present as the drug will be available in many centres if the current pattern of approval for funding from Cancer Drugs Fund continues. For this reason I think that technology could be implemented within 3 months of publication of guidance.