NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Nivolumab for treating advanced, unresectable melanoma after progression with anti-CTLA-4 therapy [ID845]

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab within its marketing authorisation for treating advanced, unresectable melanoma after progression following anti-CTLA-4 therapy.

Background

Melanoma is a cancer of the skin, which in its early stages is normally asymptomatic and, if detected early, before it has spread, can be cured by surgery. However, at presentation, around 10% of melanomas will have spread to nearby lymph nodes (stage III, of which stage IIIc disease includes tumours of varying size with extensive lymph node involvement but no metastases) or to other parts of the body (stage IV). It occurs more commonly in fair-skinned people and there is strong evidence that ultra violet exposure is causal. People with an above-average mole count, sun-sensitive skin, or a strong family history of melanoma are at increased risk.

There were 11,121 new diagnoses of melanoma in 2011 and 1781 deaths registered in the England in 2012. In the UK, more than one-third of people diagnosed with melanoma are aged less than 55 years. Approximately 20–34% of people with stage IIIc melanoma and 5–22% of those with stage IV will live longer than 5 years, with survival rates being slightly higher in women than in men.

Approximately 50% of melanomas harbour activating BRAF mutations, and over 90% of these are BRAF V600 mutations. Diagnostic tests can be used to detect the BRAF mutation, including the cobas test, generic PCR sequencing tests and other validated BRAF mutation tests.

The management of advanced melanoma is rapidly evolving, with several ongoing clinical trials, and there is uncertainty about how these treatments will be sequenced in future. Treatment for advanced, unresectable melanoma is increasingly being based upon a person's BRAF gene mutation status. For adults with previously untreated advanced unresectable or metastatic melanoma, NICE Technology Appraisal (TA) 319 recommends ipilimumab (an anti-CTLA-4 therapy) as a treatment option. Ipilimumab is also recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy (NICE TA 268). For adults with unresectable or metastatic BRAF V600 mutation-positive melanoma, NICE TA269 recommends vemurafenib, and TA321 recommends dabrafenib as

treatment options. Ipilimumab, vemurafenib and dabrafenib are only recommended if the respective companies provide the drugs at the discount agreed in the patient access schemes. Dacarbazine is also used in clinical practice for people who have received prior therapy.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1). This may activate T-cell responses and promote an anti-tumour immune response. Nivolumab is administered intravenously.

Nivolumab does not currently have a marketing authorisation in the UK for treating advanced, unresectable melanoma after progression with anti-CTLA-4 therapy. It has been studied in 1 single arm trial and 1 randomised controlled trial compared with physician's choice of either dacarbazine or carboplatin and paclitaxel in adults without BRAF V600 mutations whose disease has progressed after an anti-CTLA-4 therapy and for those with BRAF V600 mutations, whose disease has progressed after receiving both a BRAF inhibitor and an anti-CTLA-4 therapy.

Intervention(s)	Nivolumab
Population(s)	Adults with advanced, unresectable melanoma whose disease has progressed after anti-CTLA-4 therapy
Comparators	Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology appraisal 268, Dec 2012, 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'. Review proposal date Nov 2014. Technology Appraisal 321, Oct 2014, Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. Review proposal date Oct 2017. Technology appraisal 269, Dec 2012,. 'Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma.' Static list. Ongoing appraisals: Technology Appraisal in preparation, ID760, 'Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab'. Earliest anticipated date of publication Dec 2015 Technology Appraisal in preparation, ID661, 'Dabrafenib and trametinib for treating advanced unresectable or metastatic BRAFV600 mutation-positive melanoma'. Earliest anticipated date of publication June 2016 Related Guidelines: Clinical Guideline in preparation, 'Melanoma: assessment and management of melanoma'. Earliest

	anticipated date of publication July 2015. Related Interventional Procedures: Interventional procedure guidance 446, Mar 2013, 'Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma'. Review proposal date TBC. Interventional Procedure Guidance in preparation, 'Electrochemotherapy for the treatment of malignant melanoma (GID-IP1041)'. Earliest anticipated date of publication TBC. Related Public Health Guidance/Guidelines: Public health guidance 32, Skin cancer prevention: information, resources and environmental changes January 2011. Guidance under part review. Related NICE Pathways: Skin cancer NICE Pathway, published July 2014
Related National Policy	NHS England, 2013/14, NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a. NHS England, 2013/14, NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a. National Cancer Peer Review Programme, 2013, Manual for Cancer Services: Skin Measures. National Service Frameworks, Cancer Department of Health, 2013, NHS Outcomes Framework 2014-2015. Domains 1, 2, 4 and 5. Department of Health, 2011, Improving outcomes: a strategy for cancer Department of Health, 2009, Cancer commissioning guidance Department of Health, 2007, Cancer reform strategy

Questions for consultation

Have all relevant comparators for nivolumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for advanced, unresectable melanoma that has progressed after anti-CTLA-4 therapy?

Would retreatment with ipilimumab be used after progression following first-line ipilimumab therapy?

Is dacarbazine an appropriate comparator for nivolumab in this indication?

Should dabrafenib and vemurafenib be included as comparators for people with BRAF V600 mutation-positive disease who have progressed following treatment?

Are there any subgroups of people in whom nivolumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider nivolumab will fit into the existing NICE pathway, skin cancer?

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 the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which nivolumab 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 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.

Do you consider nivolumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of nivolumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's

Technology Appraisal processes is available at
http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)