NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Nivolumab for previously untreated, advanced, unresectable melanoma

Draft scope (pre-referral) [ID 846, 847, 848]

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab within its marketing authorisation for treating previously untreated advanced, unresectable melanoma.

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, approximately 12% of cutaneous 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 registered in England in 2011 and 1,781 deaths in 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 melanoma 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 as a treatment option. The guidance covers people with and without the BRAF V600 mutation. Dacarbazine is also used in clinical practice for people without the BRAF V600 mutation. 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.

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 untreated advanced, unresectable melanoma. It is being studied as monotherapy or in combination with ipilimumab compared with ipilimumab alone in people with previously untreated advanced, unresectable melanoma. It has also been compared with dacarbazine in people with previously untreated disease without a BRAF mutation. There is a planned trial of nivolumab in combination with ipilimumab followed by dabrafenib in combination with trametinib, compared with initial treatment with dabrafenib in combination with trametinib followed by nivolumab in combination with ipilimumab, for people with advanced unresectable BRAF V600 mutation-positive melanoma.

It is proposed that the appraisal of nivolumab for untreated advanced, unresectable melanoma be conducted as 3 separate single technology appraisals as follows:

- Nivolumab monotherapy for previously untreated, advanced, unresectable melanoma without a BRAF mutation (ID846)
- Nivolumab monotherapy for previously untreated, advanced, unresectable BRAF V600 mutation-positive melanoma (ID847)
- Nivolumab in combination with ipilimumab for previously untreated, advanced, unresectable melanoma (ID848)

This will allow guidance to be timely relative to the expected marketing authorisations for the different therapeutic indications. We welcome comments on the appropriateness of this approach to appraising nivolumab for previously untreated, unresectable, advanced melanoma. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)

Intervention, population and comparators for the appraisal of nivolumab monotherapy for previously untreated, advanced, unresectable melanoma without a BRAF mutation (ID846)

Intervention	Nivolumab
Population(s)	Adults with untreated advanced, unresectable melanoma without a BRAF mutation
Comparators	Ipilimumab

Questions for consultation

Have all relevant comparators for nivolumab been included in the table?

Is dacarbazine an appropriate comparator for people with untreated advanced melanoma without a BRAF mutation? Would it be considered for certain patient subgroups only (for example, people who are ineligible for, or intolerant to, ipilimumab)?

Intervention, population and comparators for the appraisal of nivolumab monotherapy for previously untreated, advanced, unresectable BRAF V600 mutation-positive melanoma (ID847)

Intervention(s)	Nivolumab
Population(s)	Adults with untreated advanced, unresectable BRAF V600 mutation-positive melanoma
Comparators	• Dabrafenib • Vemurafenib • Ipilimumab

Questions for consultation

Have all relevant comparators for nivolumab been included in the table?

Should ipilimumab be included as a comparator for previously untreated disease with a BRAF V600-positive mutation?

Intervention, population and comparators for the appraisal of nivolumab in combination with ipilimumab for previously untreated, advanced, unresectable melanoma (ID848)

Intervention(s)	Nivolumab in combination with ipilimumab
Population(s)	Adults with untreated, advanced, unresectable melanoma
Comparators	For BRAF mutation positive disease: • Dabrafenib • Vemurafenib • Ipilimumab For BRAF mutation negative disease: • Ipilimumab

Questions for consultation

Have all relevant comparators for nivolumab in combination with ipilimumab been included in the scope?

Should ipilimumab be included as a comparator for nivolumab in previously untreated disease with a BRAF V600-positive mutation?

Is dacarbazine, or any other chemotherapy, an appropriate comparator for nivolumab in people with untreated advanced unresectable melanoma without a BRAF mutation? Would it be considered for certain patient subgroups only (for example, people in whom ipilimumab is contraindicated or not tolerated)?

Outcomes, economic analysis and other considerations for the appraisal of nivolumab for previously untreated, advanced melanoma (ID846, ID847 and ID848)

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.

Other questions for consultation

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 for 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.

Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal 321, Oct 2014, 'Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma.' Review proposal date Oct 2017. Technology Appraisal 319, Jul 2014, 'Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma'. Review proposal date Jun 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. Clinical Guideline. 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, Jan 2011, 'Skin cancer prevention: information, resources and environmental changes' 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