NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Nivolumab in combination with ipilimumab for advanced, unresectable melanoma

Final scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab in combination with ipilimumab within its marketing authorisation for treating advanced, unresectable melanoma.

Background

Melanoma is a cancer of the skin. In its early stages, melanoma is normally asymptomatic and can be cured by surgery (resection). However, at presentation, approximately 10% of melanomas will have spread to nearby lymph nodes (stage III) 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 11,281 new diagnoses of melanoma and 1781 deaths registered in England in 2012. In the UK, more than one-third of people diagnosed with melanoma are aged less than 55 years. Approximately 20-73% of people with stage III melanoma (including 20-34% of people with stage IIIc) 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 often based upon the person's BRAF mutation status.

NICE Technology Appraisal (TA) 319 recommends ipilimumab as a treatment option for adults with previously untreated unresectable or metastatic melanoma and TA268 recommends ipilimumab as a treatment option for previously treated disease. For people with a BRAF V600 mutation, TA's 269 and 321 recommend vemurafenib and dabrafenib as treatment options. NICE TA 357 recommends pembrolizumab as a treatment option after disease has progressed with a BRAF V600 or MEK inhibitor (for people with the BRAF V600 mutation) or ipilimumab (for people without the BRAF V600 mutation). Ipilimumab, vemurafenib , dabrafenib and pembrolizumab are only

recommended if the respective companies provide the drugs at the discount agreed in the patient access schemes. Dacarbazine and supportive care may also be considered when ipilimumab or BRAF inhibitors are unsuitable or have already been tried.

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 in combination with ipilimumab does not currently have a marketing authorisation in the UK for treating advanced or unresectable melanoma.

Nivolumab has a marketing authorisation in the UK, as a monotherapy, for treating advanced (unresectable or metastatic) melanoma in adults.

Nivolumab is being studied in combination with ipilimumab compared with nivolumab monotherapy or ipilimumab monotherapy for people with previously untreated advanced, unresectable melanoma.

Intervention(s)	Nivolumab in combination with ipilimumab
Population(s)	Adults with advanced (unresectable or metastatic) melanoma
Comparators	• Ipilimumab • Pembrolizumab • BRAF inhibitors (dabrafenib and vemurafenib) for people with BRAF V600 mutation-positive melanoma
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 will 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 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. Technology Appraisal 268, 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'. Review proposal date Jun 2017. Technology Appraisal 357, Oct 2015. 'Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab'. Review proposal date Oct 2018. Ongoing appraisals: 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.

	Technology Appraisal in preparation, ID801. 'Pembrolizumab for treating advanced melanoma not previously treated with ipilimumab'. Earliest anticipated date of publication Nov 2015. 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
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