NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab with ipilimumab for adjuvant treatment of completely resected stage III or IV melanoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab with ipilimumab within its marketing authorisation for adjuvant treatment of completely resected stage III or IV melanoma.

Background

Melanoma is a cancer of the skin. In its early stages, melanoma is normally asymptomatic and can often be cured by surgery (resection). However, it can spread or metastasise to nearby lymph nodes or to other parts of the body . Most melanomas occur in people with pale skin. The risk factors are skin that tends to burn in the sun, having many moles, sun exposure and sunburn.

There were 13,748 new melanoma diagnoses[1] and 1,937 deaths from melanoma skin cancer[2] registered in England in 2016.

The stage of melanoma describes how deeply it has grown into the skin, and whether it has spread. At stage I and II, there is no evidence that the tumour has spread anywhere else in the body, although there is a possibility of microscopic spread. Stage III melanoma means that the melanoma cells have spread into skin, lymph vessels, or lymph glands close to the melanoma. Stage III melanomas are considered intermediate to high risk as they are more likely to spread to other distant parts of the body (stage IV melanoma) than in earlier melanoma stages. Advanced melanoma (stage IV) means the cancer has spread from where it started to another part of the body. In 2016, the proportion of people in the UK diagnosed with melanoma at stage III or IV disease was 9%[1]. Information on survival by disease stage that is specific to England is limited; data from the former Anglia Cancer Network for men and women diagnosed between 2002-2006 indicates five-year survival of approximately 50-55% for stage III disease and 8-24% for stage IV disease[3].

Surgery (tumour removal and wide local excision) is the main treatment for early (stage I) and medium stage (stage II and III) melanoma. Only a small proportion of advanced (stage IV) melanoma can be completely removed by surgery[4]. Surgical removal of the nearby lymph nodes is also considered if there is evidence of microscopic spread. Early recognition of melanoma and accurate diagnosis present the best opportunities for cure. People who have had surgery to remove stage III or IV tumours are at high risk of relapse and death; for example, 5-year relapse-free survival is 28-44% for stage III melanoma[5]. NICE technology appraisal 255 recommends nivolumab for use within the Cancer Drugs Fund as an option for the adjuvant treatment of

completely resected melanoma in adults with lymph node involvement or metastatic disease. NICE technology appraisal 553 recommends pembrolizumab for use within the Cancer Drugs Fund as an option for the adjuvant treatment of stage III melanoma with lymph node involvement in adults who have had complete resection. NICE technology appraisal 544 recommends dabrafenib with trametinib as an option for the adjuvant treatment of resected stage III BRAF V600 mutation-positive melanoma in adults.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb Pharmaceuticals) is a human immunoglobulin G4 monoclonal antibody that works by influencing how T-cells respond to cancer cells. Specifically, nivolumab binds to PD-1 (a protein found on the surface of T-cells) enabling the body to recognise and destroy tumour cells.

Ipilimumab (Yervoy, Bristol-Myers Squibb Pharmaceuticals) is a human antibody that binds to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), another molecule expressed on T-cells that plays a role in regulating natural immune responses. Ipilimumab blocks the activity of CTLA-4 improving the immune attack on cancer cells.

It is thought that when used in combination, both drugs may be more effective than when used as monotherapy. Both drugs are administered intravenously.

Nivolumab in combination with ipilimumab does not currently have a marketing authorisation in the UK for the adjuvant treatment of stage IIIb to IV completely resected melanoma. However, this treatment combination has been studied in a randomised controlled trial in patients aged 12 years and older who have had a complete surgical removal of stage IIIb/c/d or stage IV melanoma. Nivolumab in combination with ipilimumab already has a marketing authorisation for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Intervention(s)	Nivolumab with ipilimumab
Population(s)	People with completely surgically resected stage III or IV melanoma
Comparators	• For adults with stage III BRAF V600 mutation-positive disease: Dabrafenib with trametinib • For all other groups: Routine surveillance

Outcomes	The outcome measures to be considered include • overall survival • recurrence-free survival • distant metastases free survival • 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 commercial arrangements for the intervention, comparator and subsequent treatment 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: Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (2019). NICE Technology Appraisal 558. Review date to be confirmed Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (2018). NICE Technology Appraisal 553. Review date to be confirmed Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (2018). NICE Technology Appraisal 544. Review date 2021 Related Guidelines: Melanoma: assessment and management of melanoma. (2015) NICE guidelines NG14.

	Related Quality Standards: Skin cancer (2016) NICE quality standard QS130 Related NICE Pathways: Melanoma (2017) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 to 5 https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 Department of Health (2014) The national cancer strategy: 4th annual report Department of Health (2011) Improving outcomes: a strategy for cancer

Questions for consultation

Have all relevant comparators for nivolumab with ipilimumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for completely resected stage III or IV melanoma?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom nivolumab with ipilimumab is expected to be more clinically effective and cost effective or other groups that should be examined separately, for example would it be appropriate to consider subgroups by stage of disease?

Where do you consider nivolumab with ipilimumab will fit into the existing NICE pathway for Melanoma?

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 with ipilimumab 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 with ipilimumab 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 with ipilimumab 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.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

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).

References

1 Cancer Research UK (2016) Melanoma skin cancer incidence statistics. Accessed August 2019

https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer/incidence#heading-Zero

2 Cancer Research UK Melanoma skin cancer mortality statistics. Accessed August 2019

https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer/mortality#heading-Zero

3 Cancer Research UK Melanoma skin cancer survival statistics. Accessed August 2019

https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer/survival#heading-Three

4. Stage IV melanoma: completely resectable patients are scarce. Wevers and Hoekstra. Ann Surg Oncol. 2013 Jul;20(7):2352-6

5. Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe – a systematic review of the literature. Svedman et al. Clinical Epidemiology. 2016; 8:109-22