NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of nivolumab-relatlimab within its marketing authorisation for untreated unresectable or metastatic melanoma.

Background

Cutaneous 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 (metastasise) to nearby lymph nodes (stage 3) or other parts of the body (stage 4). Most melanomas occur in people with pale skin. The risk factors are skin that tends to burn in the sun, having many moles, intermittent sun exposure and sunburn.[1]

In England in 2017, there were 13,740 registrations of newly diagnosed cases of malignant melanoma of the skin.[2] In the same year, England and Wales recorded 2,106 deaths with malignant melanoma of the skin as the underlying cause.[3] Approximately 50% of melanomas harbour activating BRAF mutations.[4]

NICE technology appraisal 319 recommends ipilimumab as an option for previously untreated unresectable or metastatic melanoma. In addition, NICE technology appraisals 366, 384 and 400 recommend pembrolizumab (for melanoma that has not previously been treated with ipilimumab), nivolumab, and nivolumab with ipilimumab as treatment options, respectively. For people with BRAF mutation-positive melanoma, NICE technology appraisals 269, 321, 396 and 562 recommend vemurafenib, dabrafenib, trametinib with dabrafenib, and encorafenib with binimetinib as treatment options, respectively. NICE guideline 14 recommends immunotherapy with nivolumab plus ipilimumab. Pembrolizumab or nivolumab are suitable only when nivolumab plus ipilimumab is unsuitable or unacceptable, for example due to potential toxicity. When immunotherapy is contraindicated or unsuitable, targeted therapies encorafenib plus binimetinib, or dabrafenib plus trametinib are recommended. Dabrafenib or vemurafenib is suitable when binimetinib and trametinib are contraindicated. When targeted treatment is contraindicated, dacarbazine chemotherapy or best supportive care is recommended.

The technology

Nivolumab-relatlimab (Opdualag, Bristol-Myers Squibb) does not have a UK marketing authorisation for untreated unresectable or metastatic melanoma.

It has been studied in a randomised clinical trial compared with nivolumab monotherapy in adults and adolescents 12 years of age and older with previously untreated unresectable or metastatic melanoma.

Intervention(s)	Nivolumab-relatlimab
Population(s)	People aged 12 years and older with previously untreated unresectable or metastatic melanoma
Subgroups	If the evidence allows the following subgroups will be considered: • programmed death ligand 1 (PD-L1) expression (≥1% or <1%); • BRAF V600 mutation status;
Comparators	• Nivolumab • Nivolumab with ipilimumab • Pembrolizumab • Trametinib with dabrafenib • Encorafenib with binimetinib
Outcomes	The outcome measures to be considered include: • progression-free survival • overall 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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. 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. The availability of any managed access arrangement for the intervention will be taken into account. The economic modelling should include the costs associated with diagnostic testing for PD-L1 expression in people with melanoma who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).
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	**Related Technology Appraisals:** Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (2019) NICE Technology Appraisal 562. Review date 2022 Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (2016) NICE Technology Appraisal 414. Review date to be confirmed. Nivolumab in combination with ipilimumab for treating advanced melanoma (2016) NICE Technology Appraisal 400. Review date to be confirmed. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (2016) NICE

	Technology Appraisal 396. Review date to be confirmed. Nivolumab for treating advanced (unresectable or metastatic) melanoma (2016) NICE Technology Appraisal 384. Review date to be confirmed. Pembrolizumab for advanced melanoma not previously treated with ipilimumab (2015; updated 2017) NICE Technology Appraisal 366. Review date to be confirmed. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (2014) NICE Technology Appraisal 321. Review date to be confirmed. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (2014) NICE Technology Appraisal 319. Review date to be confirmed. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (2012; updated 2015) NICE Technology Appraisal 269. Review date to be confirmed. **Related Guidelines:** Melanoma: assessment and management (2015; updated 2022) NICE guideline NG14. Improving outcomes for people with skin tumours including melanoma (2006, updated 2010) NICE guideline CSG8 **Related Interventional Procedures:** Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (2013). NICE interventional procedures guidance 446. **Related Quality Standards:** Skin cancer (2016;updated 2022). NICE quality standard 130
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 and 3. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 NHS Standard Contract for Cancer: Skin (Adult) Section B Part 1 – Service Specifications (2013).

Questions for consultation

Where do you consider nivolumab-relatlimab will fit into the existing care pathway for untreated unresectable or metastatic melanoma?

- Have all relevant comparators for nivolumab-relatlimab been included in the scope?

- Is it appropriate to exclude the BRAF inhibitor monotherapies (dabrafenib and vemurafenib) as comparators for people with BRAF V600 mutation-positive melanoma?
- Is ipilimumab monotherapy an appropriate comparator?
- Are the proposed subgroups appropriate?

Would nivolumab-relatlimab be a candidate for managed access?

Do you consider that the use of nivolumab-relatlimab can result in any potential 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 committee to take account of these benefits.

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/relatlimab 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.

NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

NICE's health technology evaluations: the manual states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost-comparison methodology for this topic?

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1. Cancer Research UK (2020) Risks and causes of melanoma. Accessed July 2021

2. Office for National Statistics (2019). Cancer registration statistics, England 2017 dataset. Accessed July 2021

3. Office for National Statistics (2018). Death registrations summary tables - England and Wales 2017 dataset. Accessed July 2021

4. Ascierto, Paolo A et al. "The role of BRAF V600 mutation in melanoma." *Journal of translational medicine* vol. 10 85 (2012).

5. NHS (2020) Skin cancer (melanoma) – overview. Accessed July 2021