NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Atezolizumab with cobimetinib and vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of atezolizumab with cobimetinib and vemurafenib within its marketing authorisation for treating unresectable or metastatic BRAF V600 mutation-positive 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 (stage III) or to other parts of the body (stage IV). 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.

A mutated form of the BRAF gene is found in 40% to 60% of melanomas; 80% to 90% of these are BRAF V600 mutations.[3] Mutated BRAF genes activate the RAF-MEK-ERK pathway, leading to uncontrolled cell division and growth of the tumour.

Treatment options for advanced melanoma depend on the person's BRAF mutation status and treatment history. A BRAF inhibitor and immunotherapy are both options for treating BRAF mutation-positive advanced melanoma with people unable to receive immunotherapies due to performance status and frailty receiving targeted therapies instead.

For BRAF V600 mutation-positive unresectable or metastatic melanoma, NICE technology appraisal (TA) guidance recommends the BRAF inhibitor, dabrafenib alone (TA321) or with the MEK inhibitor, trametinib (TA396) and the BRAF inhibitor, vemurafenib alone (TA269). BRAF inhibitor encorafenib with MEK inhibitor binimetinib (TA562) alongside dabrafenib with trametenib is considered the standard of care in clinical practice, replacing the use of targeted BRAF inhibitor monotherapy. NICE technology appraisal guidance 414 does not recommend the use of vemurafenib with the MEK inhibitor, cobimetinib, for treating BRAF V600 mutation-positive advanced melanoma.

Treatment of advanced melanoma with immunotherapies is effective regardless of BRAF mutation status. NICE Technology Appraisal (TA) guidance recommends nivolumab alone (TA384) and in combination with ipilimumab (TA400) for treating advanced melanoma. Ipilimumab monotherapy is recommended both for previously untreated (TA319) or

previously treated (TA268) unresectable or metastatic melanoma. For people not previously treated with ipilimumab, pembrolizumab alone (TA366) is recommended for treating advanced melanoma. Pembrolizumab is also recommended after disease progression with ipilimumab (TA357) for treating advanced melanoma.

The technology

Atezolizumab Tecentriq, Roche) is a humanised, anti-programmed cell death ligand-1 (PD-L1) monoclonal antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. Cobimetinib (Cotellic, Roche) inhibits the action of the abnormal BRAF protein, with the aim of slowing the growth and spread of the cancer. Vemurafenib (Zelboraf, Roche) inhibits the oncogenic BRAF V600 protein kinase. BRAF is part of the MAPK signalling pathway, which helps to control the proliferation, differentiation and apoptosis of cells. Atezolizumab is administered by intravenous infusion whereas cobimetinib and vemurafenib are administered orally.

Atezolizumab with cobimetinib and vemurafenib does not currently have a marketing authorisation in the UK for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. It is being studied in a clinical trial comparing atezolizumab plus cobimetinib and vemurafenib with placebo plus cobimetinib and vemurafenib in previously untreated adults with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Intervention(s)	Atezolizumab with cobimetinib and vemurafenib
Population(s)	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma

Comparators	Targeted monotherapies: • Dabrafenib • Vemurafenib Targeted combination therapies: • Encorafenib with binimetinib • Dabrafenib with trametinib Immuno- monotherapies: • Nivolumab • Ipilimumab • Pembrolizumab Immuno-combination therapies: • Nivolumab with ipilimumab • Pembrolizumab after ipilimumab
Outcomes	The outcome measures to be considered include: • progression free survival • overall survival • response rates • 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.

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: 'Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma' (2019). NICE Technology Appraisal 562. Review date February 2022. 'Nivolumab for treating advanced (unresectable or metastatic) melanoma' (2016) NICE technology appraisal guidance 384. Review date February 2019 'Nivolumab in combination with ipilimumab for treating advanced melanoma' (2016) NICE technology appraisal guidance 400. Review date July 2019. 'Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma' (2016). NICE Technology Appraisal 396. Review date June 2019. 'Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma' (2016). NICE Technology Appraisal 414. Review date October 2019. 'Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab' (2015) NICE technology appraisal guidance 357. Review date September 2018. 'Pembrolizumab for advanced melanoma not previously treated with ipilimumab' (2015) NICE technology appraisal guidance 366. Review date November 2018. 'Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma' (2014) NICE technology appraisal guidance 319. Review date July 2017 'Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma' (2014). NICE Technology Appraisal 321. Static list. 'Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma' (2012). NICE Technology Appraisal 269. Static list.

	Related Guidelines: 'Melanoma: assessment and management' (2015) NICE guideline NG14. Review date to be confirmed. 'Improving outcomes for people with skin tumours including melanoma' (2006) NICE Cancer Service guideline CSG8. Review date March 2018. Related Quality Standards: 'Skin cancer' (2016) NICE quality standard 130. Related NICE Pathways: Melanoma (2016) NICE pathway. http://pathways.nice.org.uk/
Related National Policy	NHS England, Manual for prescribed specialised services 2017/18: 105 – Specialist cancer services (adults) Department of Health, Improving Outcomes: A Strategy for Cancer, fourth annual report, Dec 2014 Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1, 2, 4 and 5.

Questions for consultation

Which treatments are considered to be established clinical practice in the NHS for unresectable or metastatic BRAF V600 mutation-positive melanoma?

- Would targeted therapies be considered for people who receive immunotherapies first-line?
- Are people treated with either targeted therapy or immuno-monotherapies likely to then be considered for treatment with combination therapies Would atezolizumab with cobimetinib and vemurafenib be used after treatment with immunotherapy and targeted therapy options in clinical practice?

Have all relevant comparators for atezolizumab in combination with cobimetinib and vemurafenib been included in the scope?

Are the outcomes listed appropriate?

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

Where do you consider atezolizumab in combination with cobimetinib and vemurafenib will fit into the existing NICE pathway, 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 atezolizumab in combination with cobimetinib and vemurafenib 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 atezolizumab with cobimetinib and vemurafenib 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 atezolizumab with cobimetinib and vemurafenib 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).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost

comparison case is made. We welcome comments on the appropriateness and suitability of the cost comparison methodology to 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. Vora NL. (2016) Melanoma and BRAF. Medscape. Accessed January 2018.