NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab with temozolomide and radiotherapy for newly diagnosed glioblastoma with MGMT methylation

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab with temozolomide and radiotherapy within its marketing authorisation for newly diagnosed MGMT-methylated glioblastoma multiforme.

Background

Gliomas are the most common type of primary brain tumour. They develop from the glial cells that support the nerve cells of the brain and spinal cord. Gliomas are graded according to their likely growth rate, from grade 1 (slowest growing) to grade 4 (fastest growing). Grade 1 or 2 tumours are considered 'low-grade' and usually classed as benign or non-cancerous, although they may transform into malignant tumours. Grade 3 and 4 tumours, known as 'high-grade', are malignant and have a worse prognosis. Glioblastoma, a grade 4 glioma is the most aggressive type of brain tumour. The types of glioma are further identified by the cells they develop from (astrocytoma, ependymoma and oligodendroglioma) and increasingly, by molecular genetics such as IDH status and 1p/19q codeletions.

Symptoms of glioblastoma depend on the size, location, and degree of infiltration of the tumour. They include headache, nausea, vomiting, seizure, visual disturbance, speech and language problems and changes in cognitive or functional ability. Scales of performance status, such as the World Health Organisation (WHO) performance status, can be used to categorise functional ability with glioblastoma.

In 2015, about 2,500 people were diagnosed with glioblastoma in England.[1] The average age of diagnosis is 55 years.[2] Between 2010 and 2011, 40% of adults with brain cancer in England and Wales survived for 1 year or more and 19% survived for 5 years or more.[3]

Glioblastoma is usually treated by surgical resection if possible, which may achieve either complete or partial resection of the tumour, although complete resection is rare. Treatment decisions take into account Karnofsky performance status, time from last treatment and tumour molecular markers, for example, MGMT methylation.

For people with newly diagnosed glioblastoma, following surgery or if surgery is not possible, NICE's guideline for brain tumours (primary) and brain

metastasis in adults recommends: radiotherapy with temozolomide, temozolomide alone, radiotherapy alone, hypofractionated radiotherapy or best supportive care alone.

NICE technology appraisal guidance 121 recommends temozolomide for newly diagnosed glioblastoma multiforme in patients with a World Health Organization (WHO) performance status of 0 or 1. It also recommends carmustine implants for newly diagnosed high-grade glioma in patients in whom 90% or more of the tumour has been resected.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a fully humanised monoclonal antibody that specifically binds to anti-programmed cell death-1 (PD-1) receptor on the surface of immune cells and restores T-cell activity by blocking the inhibitory pathway with PD-L1. It is administered intravenously.

Nivolumab does not have a marketing authorisation for treating glioblastoma. It has been studied in a clinical trial in combination with temozolomide and radiation therapy in adults with newly diagnosed MGMT methylated glioblastoma compared with temozolomide plus radiation therapy.

Intervention(s)	Nivolumab with temozolomide plus radiation therapy
Population(s)	People with newly diagnosed glioblastoma with MGMT methylation.
Comparators	• Radiation therapy with temozolomide • Radiation therapy alone • Hypofractionated radiotherapy • Carmustine implants (only for people in whom 90% or more of the tumour has been resected) • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free 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. 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.
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. If evidence allows, subgroup analyses by molecular markers will be considered, for example, IDH status.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (2007). NICE Technology Appraisal 121. Static list. **Appraisals in development (including suspended appraisals):** Asunercept for treating glioblastoma. NICE technology appraisal guidance [ID1301]. Publication date to be confirmed. DCVax-L for treating newly diagnosed glioblastoma multiforme. NICE technology appraisal guidance [ID836]. Publication date: suspended. Depatuxizumab mafodotin in combination for untreated EGFR-amplified glioblastoma. NICE technology appraisal guidance [ID1466]. Publication date to be confirmed. Glioblastoma - bevacizumab. NICE technology appraisal guidance. Publication date: suspended. **Related Interventional Procedures:** Photodynamic therapy for brain tumours (2009). NICE interventional procedures guidance 290.

	Related Guidelines: Brain tumours (primary) and brain metastases in adults (2018). NICE guideline 99. Publication date: July. Improving outcomes for people with brain and other central nervous system tumours (2006). NICE cancer service guideline 10. Reviewed March 2017, incorporated into NICE guideline 99. **Related NICE Pathways:** Brain cancer: glioma NICE pathway
Related National Policy	NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 105. NHS England protocol for emergency surgical interventions in patients with a brain tumour v3 (2018) NHS England standard contract for cancer: brain/central nervous system, adult (2013/14) Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domain 1. The NHS Long Term Plan, 2019. NHS Long Term Plan

Questions for consultation

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

Which treatments are considered to be established clinical practice in the NHS for glioblastoma? Does treatment differ depending on whether the tumour has MGMT methylations or not? If so, how?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other 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, brain tumours and metastases?

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.

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.

- 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 Brain, other CNS and intracranial tumours incidence statistics. Accessed January 2019.

2. Patient UK. Gliomas and glioblastoma multiforme. Accessed January 2019.

3. Cancer Research UK Brain, other CNS and intracranial tumours survival statistics. Accessed January 2019.