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Nivolumab in addition to temozolomide and radiotherapy for MGMT-methylated glioblastoma in newly diagnosed adults - first line

NIHRIO ID	12643	**NICE ID**	9426
Developer/Company	Bristol-Myers Squibb Pharmaceuticals Ltd	**UKPS ID**	646337

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Nivolumab in addition to temozolomide and radiotherapy is being investigated as a treatment option for adult patients newly diagnosed with MGMT-methylated glioblastoma. Glioblastoma is a fast-growing type of brain tumour and the MGMT-methylated status can help to predict how some patients might respond to treatment. MGMT-methylated glioblastoma is an aggressive brain cancer that typically results in death within months following diagnosis if not treated. Current therapies remain palliative and include surgery to remove as much of the tumour as possible, followed by chemotherapy and/or radiotherapy.

Nivolumab is a type of immunotherapy that is currently licensed in the UK for the treatment of several types of advanced cancers such as melanoma, non-small cell lung cancer, and kidney cancer. It blocks a protein called programmed death-1 (PD-1), which is found on the surface of a type of immune cells called T-cells. Blocking PD-1 stimulates the T-cells to kill the cancer cells. Temozolomide in combination with radiotherapy is currently licensed in the UK for newly diagnosed glioblastoma in adults. The addition of nivolumab to temozolomide and radiotherapy will potentially offer an additional first line treatment option for adult patients who are newly diagnosed MGMT-methylated glioblastoma.

PROPOSED INDICATION

Newly-diagnosed methylated MGMT glioblastoma multiforme, in addition to temozolomide and radiotherapy – first line.[a]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with its two ligands, namely PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion.Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[1]

Nivolumab in addition to temozolomide and radiotherapy is in phase III stage of development for the first line treatment of newly diagnosed adult patients with MGMT-methylated Glioblastoma.[a] In the phase III clinical trial (CheckMate548; NCT02667587), Nivolumab intravenous (IV) infusion is given at specified dose on specified days; Temozolomide 75 mg/meter squared orally is given daily during radiotherapy, 4 week treatment break, 150 mg/meter squared on day 1-5 for cycle 1 and increased to 200 mg/meter squared day 1-5 for cycle2-cycle 6 as tolerated; (additional cycles may be permitted with approval of sponsor). Radiotherapy 2 gray units (joule of radiation energy per kilogram) is given 5 times per week for 6 weeks.[2]

INNOVATION AND/OR ADVANTAGES

Glioblastoma is the most common primary central nervous system (CNS) tumour and is the most aggressive neoplasm among gliomas. Glioblastoma represents a high unmet medical need due to its dismal prognosis, meaningful disability and lack of new agents since temozolomide concurrent with and adjuvant to radiotherapy became the standard therapy. Treatment of glioblastoma remains challenging. The breakthrough of immune oncology is still awaited by glioblastoma patients and oncologists. Improvement in safety and tolerability will have a key role for such therapies to take over in glioblastoma patients, as well as combinations of promising approaches.[3]

Nivolumab, a PD-1 blocking antibody, is indicated for the treatment of several types of cancers such as melanoma, non-small cell lung cancer, squamous cell cancer of the head and neck, renal cell carcinoma and urothelial carcinoma.[1, 4] Expression of PD-L1 has been observed in primary glioblastoma tumours, and expression levels were found to correlate with glioma grade. Furthermore, treatment with immune checkpoint inhibitors demonstrated improved survival in murine models of glioma and was able to provide disease control (stable disease or better) in some patients with melanoma who had brain metastases, suggesting that immunotherapy could be a potential treatment option for patients with CNS tumours.[5]

[a] Information provided by Bristol-Myers Squibb on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab in addition to temozolomide and radiotherapy does not currently have Marketing Authorisation in the EU/UK for any indication.

Nivolumab is licensed in the EU/UK for adults as follows:[4,6]

- Unresectable or metastatic advanced melanoma in combination with ipilimumab
- First-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma in combination with ipilimumab
- As a monotherapy for:
  - Unresectable or metastatic advanced melanoma
  - Adjuvant treatment of melanoma
  - Previously treated advanced renal cell carcinoma
  - Locally advanced or metastatic non-small cell lung cancer
  - Locally advanced unresectable or metastatic urothelial carcinoma
  - Squamous cell cancer of the head and neck
  - Relapsed or refractory classical Hodgkin lymphoma

The most common side effects with nivolumab (which may affect more than 1 in 10 people) include tiredness, diarrhoea, nausea (feeling sick), rash and itching, pain in joints, muscles and bones, and hypothyroidism (an underactive thyroid gland), most of which are mild to moderate in severity. Nivolumab is also commonly associated with side effects related to the activity of the immune system on body organs. Most will go away with appropriate treatment or on stopping nivolumab.[7]

Nivolumab is currently in phase III clinical trials for several types of cancers including newly diagnosed patients with MGMT-unmethylated glioblastoma, hepatocellular carcinoma, Hodgkin's lymphoma, and renal cell carcinoma.[8] Nivolumab is also in phase II clinical trials for several types of cancers including follicular cell lymphoma, non-Hodgkin's lymphoma, and non-small cell lung cancer.[9]

PATIENT GROUP

DISEASE BACKGROUND

Glioma is a tumour of glial cells, the cells that support the nerve cells of the brain. Gliomas comprise a heterogeneous group of neoplasms that differ in location within the CNS, in relation to age and sex distribution, growth potential, the extent of invasiveness, morphological features, tendency for progression, and in response to treatments. Glioblastomas primarily affect adults, and they are located preferentially in the cerebral hemispheres[10] . One type of glioma is called astrocytoma which develops from astrocytes, cells that provide the brain's framework and help control the chemistry of brain cells. Glioblastoma is the most malignant (grade 4) astrocytoma[11] Glioblastoma is the most common type of malignant brain tumour[10]

Glioblastomas can be classified as primary or secondary tumours. Primary glioblastoma accounts for the vast majority of cases (60%) in adults older than 50 years. These tumours manifest de novo (i.e. without clinical or histopathologic evidence of a pre-existing, less-malignant precursor lesion), presenting after a short clinical history, usually of less than 3 months. Secondary glioblastomas, which account for 40% of cases in adults aged over 50, typically develop in younger patients (aged under 45 years) through malignant progression from a low-grade astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III). The time required for this progression varies considerably, ranging from less than 1 year to more than 10 years, with a mean interval of 4-5 years.[10]

O-6-methylguanine DNA methyltransferase (MGMT) is a protein, unique in its ability to repair DNA adducts (segments of DNA bound to cancer causing chemicals) and to self-inactivate. MGMT has recently been linked to the therapeutic success of alkylating agent chemotherapy, specifically temozolomide treatment. Low levels of functional MGMT have been correlated with success of treatment, while high levels bring about failure of therapy.[12]

Glioblastomas are more common in older adults and tend to affect men more than women. Glioblastoma multiforme usually spreads quickly to other parts of the brain, with tentacle-like projections, making complete surgical removal more difficult. It is common for glioblastomas to recur after initial treatment.[13] Current therapies remain palliative and include surgery to remove as much of the tumour as possible, followed by chemoradiation.[14]

Without therapy, patients with glioblastomas usually die within 3 months. Patients treated with optimal therapy, including surgical resection, radiation therapy, and chemotherapy, have a median survival of approximately 12 months, with fewer than 25% of patients surviving up to 2 years and fewer than 10% of patients surviving up to 5 years.[10]. Although this tumour can occur in all age groups, including children, the average age at which it is diagnosed is 55 years. The cause of these tumours is unknown. Scientists are conducting environmental, occupational, and genetic research to better understand tumour growth.[15]

Symptoms often begin abruptly, may be different in different people and may vary depending on the size, location and degree of infiltration of the tumour. Common symptoms include headaches that may be associated with vomiting, seizures or 'fits', memory loss, visual disturbance, speech and language problems, and changes in cognitive and/or functional ability. Functional ability of patients can be categorised using scales of performance status, such as the WHO performance status classification.[15, 16]

CLINICAL NEED AND BURDEN OF DISEASE

Brain tumours are relatively rare and are most common in older people. Around 25% of brain tumours in the UK each year are diagnosed in people aged 75 or older. This includes tumours in other parts of the central nervous system and tumours anywhere else inside the bones of the head.[17] In the UK in 2015, the proportion of brain tumours in relation to all cancer cases was of 3%.[18]

In England in 2016 there were a total of 4,516 registrations of newly diagnosed cases of malignant neoplasm of brain (ICD-10 codes C71). Directly age-standardised rates were 10.4 per 100,000 and 7.0 per 100,000 in males and females respectively.[19] Around 55% of malignant brain tumours (WHO grades 3 - 4) are glioblastoma multiforme (GBM), with about 2,200 cases diagnosed each year in England. More men (about 1,300) than women (about 900) are diagnosed each year with GBM.[20] Methylation of the MGMT promoter is found in 35%–45% of malignant gliomas (WHO grades 3 and 4).[21] This equates to approximately 770 to 990 of the GBM cases diagnosed each year in England.

In England in 2017/2018 there were 16,971 hospital admissions with a primary diagnosis of neoplasm of brain (ICD-10 code C71) resulting in 22,419 finished consultant episodes (FCE), 93,022 FCE bed days and 7,826 day cases.[22]

Across the UK, the incidence rate of brain, other CNS and intracranial tumours is expected to increase from 20.69 per 100,000 European age-standardised rate (EASR) (10,525 cases) in 2014 to 22.02 per 100,000 EASR (14,281.45 cases) in 2035.[23]

GBM has an extremely poor prognosis; survival times are close to the worst of any cancer (median survival is about 6 months). Median survival is statistically significantly worse for women (5.6 months) than for men (6.5 months). But longer-term survival (15 months and over) in women is as good as or better than longer-term survival in men.20

In England and Wales in 2016 there were a total of 3,822 deaths where malignant neoplasm of brain (ICD-10 code C71) was recorded as the underlying cause.[24] Latest published survival statistics (2016, patients diagnosed in 2011-2015) report a 1-year survival rate of 37.5% and 5-year survival rate of 11.5% (age-standardised).[25]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Treatment of glioblastoma usually consists of surgical resection if possible, which may achieve either complete or partial resection of the tumour, although complete resection is rare. After surgery, radiotherapy with or without chemotherapy is used. If the size and/or position of the tumour means surgery is not possible without damaging surrounding tissue, radiotherapy and/or chemotherapy is offered.[26]

CURRENT TREATMENT OPTIONS

In England, NICE recommends:

- Temozolomide as an option for the treatment of newly diagnosed glioblastoma multiforme (GBM) in patients with a World Health Organization (WHO) performance status of 0 or 1 (where 0 refers to persons able to carry out all normal activity without restriction and 1 or a person restricted in strenuous activity but ambulatory and able to carry out light work).[27]
- Carmustine implants as an option for the treatment of newly diagnosed high-grade glioma only for patients in whom 90% or more of the tumour has been resected.[27]

PLACE OF TECHNOLOGY

If licensed, nivolumab in addition to temozolomide plus radiotherapy for will offer an additional first line treatment option for adult patients who are newly diagnosed MGMT-methylated glioblastoma.

CLINICAL TRIAL INFORMATION

Trial	**CheckMate 548, NCT02667587; nivolumab vs. placebo, both in combination with temozolomide and radiotherapy; phase III**
Sponsor	Bristol-Myers Squibb
Status	Ongoing
Source of Information	Trial registry[2]
Location	EU (incl. UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled, parallel assignment
Participants	n= 693 (planned); aged 18 years and older; glioblastoma (GBM); newly diagnosed; MGMT methylated or indeterminate tumour subtype; Karnofsky performance status of ≥ 70, substantial recovery from surgery resection.

Schedule	Randomised to nivolumab specified dose IV on specified days; or placebo specified dose IV on specified days; both in combination with temozolomide 75 mg/meter squared orally daily during radiotherapy, 4 week treatment break, 150 mg/meter squared on day 1-5 for cycle 1 and increased to 200 mg/meter squared day 1-5 for cycle2-cycle 6 as tolerated; (additional cycles may be permitted with approval of sponsor); and radiotherapy 2 gray units (joule of radiation energy per kilogram) 5 times per week for 6 weeks.
Follow-up	Active treatment period and overall follow-up period are not specified.
Primary Outcomes	Overall survival (OS). [Time frame: approximately 69 months after first patient first visit]
Secondary Outcomes	Time frame: approximately 69 months after first patient first visit • Progression free survival (PFS) • Correlation of PFS and OS
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as February 2022

ESTIMATED COST

Nivolumab is already marketed in the UK. The NHS indicative price for nivolumab solution for infusion is as follows:[28]

- Opdivo 100mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £1097.00 (Hospital only).
- Opdivo 240mg/24ml concentrate for solution for infusion (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £2633.00 (Hospital only)
- Opdivo 40mg/4ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £439.00 (Hospital only).

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Asunercept for treating glioblastoma (GID-TA10227). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Glioblastoma – bevacizumab (GID-TAG413). Expected date of issue to be confirmed.
- NICE technology appraisal. Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (TA121). June 2007.
- NICE clinical guideline in development. Brain tumours (primary) and brain metastases in adults (NG 99). Published July 2018.
- NICE clinical guideline. Improving outcomes for people with brain and other central nervous system tumours (CSG10). June 2006.

- NICE interventional procedure guidance. Photodynamic therapy for brain tumours (IPG290). Published March 2009.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Brain/Central nervous system (Adult). B13/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- Stupp R, et al. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2014.[29]

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