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EVIDENCE BRIEFING
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Nivolumab in addition to radiation therapy for glioblastoma – first line

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Developer/Company	Bristol-Myers Squibb Pharmaceuticals Ltd	**UKPS ID**	641219

SUMMARY

Nivolumab in addition to radiation therapy is being investigated as a treatment option for patients newly diagnosed with glioblastoma. Glioblastoma is a fast-growing type of brain tumour that develops from glial cells in the brain. It is an aggressive brain cancer that typically results in death within months following diagnosis if not treated. Brain cancers are the ninth most common cancers in the UK; glioblastoma is one of the most common types of brain cancer. Current therapies remain palliative and include surgery to remove as much of the tumour as possible, followed by chemotherapy and/or radiation therapy.

Nivolumab is an immunotherapy product that is currently licensed in the EU/UK for the treatment of several types of advanced cancers such as melanoma, non-small cell lung cancer, and kidney cancer. It is a monoclonal antibody that acts by preventing the inhibition of T-cells (part of the body's immune system that fight cancer) through binding to a protein called programmed cell death 1 (PD-1). If licensed, nivolumab in combination with radiation therapy will offer an additional first-line treatment option for patients with glioblastoma.

PROPOSED INDICATION

Newly diagnosed adult patients with glioblastoma (un-methylated) - in combination with radiation therapy.[1]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo®) is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death 1 (PD-1) receptor and selectively blocks interaction with its programmed death ligands PD-L1 and PD-L2. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumour tissue. The inhibitory effect of PD-1 and its ligands occurs through the promotion of apoptosis in antigen specific T-cells while simultaneously blocking apoptosis in suppressor T-cells. Blocking PD-1 activity has been shown to lead to decreased tumour growth in mouse tumour models.[2]

Nivolumab in combination with radiation therapy is being investigated for the treatment of newly diagnosed adult patients with un-methylated MGMT GBM. In the phase III clinical trial (NCT02617589 CheckMate 498), patients initially received radiation therapy in the dose of 2 Gy five times a week for 6 weeks combined with intravenous infusion of nivolumab 240 mg once every 2 weeks for 16 weeks, followed by a maintenance dose of 480 mg once every 4 weeks.[1a]

INNOVATION AND/OR ADVANTAGES

Glioblastoma represents a highly unmet medical need due to its dismal prognosis, meaningful disability and lack of new agents. Immunotherapy seems to have an acceptable safety and tolerability profile in the recurrent setting and is under investigation in clinical trials in newly diagnosed glioblastoma patients.[3] Nivolumab is an immunotherapy product that is currently licensed in the EU/UK for the treatment of several types of advanced cancers such as melanoma, non-small cell lung cancer, and kidney cancer.[4]

Data from a phase III clinical trial (NCT02017717, CheckMate 143) for nivolumab in combination with radiation with or without temozolomide for patients with newly diagnosed glioblastoma suggests that the treatment is well tolerated. Rapid accrual in this study supports the feasibility of conducting the trial CheckMate 498 for nivolumab in combination with radiation therapy in patients with newly diagnosed un-methylated MGMT glioblastoma without temozolomide.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab as monotherapy is currently licensed in the UK for several malignant conditions. Nivolumab in combination with radiation therapy does not currently have Marketing Authorisation in the EU/UK for any indication.[4]

Common or very common adverse effects of nivolumab are: abdominal pain; alopecia; arthralgia; blurred vision; colitis; constipation; cough; decreased appetite; diarrhoea; dizziness; dry eyes; dry mouth; dry skin; dyspnoea; erythema; headache; hyperglycaemia; hypertension; infusion-related reactions; malaise; musculoskeletal pain; nausea; oedema; peripheral neuropathy; pneumonitis;

[a] Information provided by company

pruritus; pyrexia; rash; stomatitis; thyroid disorders; upper respiratory tract infection; vitiligo; vomiting.[4]

Nivolumab as monotherapy and in combination with other therapies is currently in phase III stage of development for a range of different types of cancers including methylated glioblastoma.[6]

PATIENT GROUP

DISEASE BACKGROUND

Glioblastoma is a malignant glioma (WHO grade IV). Glioblastoma is the most common and most malignant type of brain tumour. Gliomas comprise a heterogeneous group of neoplasms that differ in location within the central nervous system, 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.[7]

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.[7]

MGMT (tumour O-6-methylguanine DNA methyltransferase) is a protein unique in its ability to repair DNA adducts (segments of DNA bound to cancer causing chemicals) and to self-inactivate. Loss of MGMT expression has been reported to occur in many tumour types, including glioma, lymphoma, breast and prostate cancer, as well as retinoblastoma.[8] Methylation of the MGMT promoter is found in 35%–45% of malignant gliomas. The median survival for patients with a methylated MGMT promoter has been reported as 21.7 months compared with 12.7 months for patients without.[9,10]

Symptoms of glioblastoma depends on the size, location and degree of infiltration of the tumour. They include headache, nausea, vomiting, seizures, 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.[11]

Glioblastoma usually spreads quickly and invades 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.[12] Current therapies remain palliative and include surgery to remove as much of the tumour as possible, followed by chemoradiation. [13] 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.[7]

CLINICAL NEED AND BURDEN OF DISEASE

Brain tumours are relatively rare. In the UK in 2015, the proportion of brain tumours in relation to all cancer cases was of 3%.[14]

In England in 2016 there were a total of 9,273 registrations of newly diagnosed brain cancer, other central nervous system and intracranial tumours (ICD-10 codes C70 to C75).[15] Glioblastoma is the most common type of malignant brain tumour. Around 55% of all brain tumours are glioblastomas[16] and applying that proportion to the total number of brain cancers would equate to a total of ~5,100 cases of glioblastomas in England in 2016.

Across the UK, the incidence rate 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.[17]

In England and Wales in 2016 there were a total of 3,828 deaths where malignant neoplasm of brain (ICD-10 code C71) was recorded as the underlying cause.[18] 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).[19]

In England in 2016/2017 there were 16,202 hospital admissions with a primary diagnosis of neoplasm of brain (ICD-10 code C71) resulting in 99,423 bed days and 7,135 day cases.[20]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

In the UK, 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 or position of the tumour means surgery is not possible without damaging surrounding tissue, radiotherapy and/or chemotherapy is offered.[21]

CURRENT TREATMENT OPTIONS

In England, NICE recommends temozolomide as an option for treating newly diagnosed glioblastoma in people with a 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).[22] It also recommends carmustine implants for newly diagnosed high-grade glioma, but only for people in whom 90% or more of the tumour has been resected.[23]

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with radiation therapy will offer an additional first-line treatment option for patients with newly diagnosed un-methylated MGMT glioblastoma.

CLINICAL TRIAL INFORMATION

Trial	CheckMate 498, NCT02617589, 2015-003739-37; 18 years and older; nivolumab vs temozolomide, both in combination with radiation; phase III
Sponsor	Bristol-Myers Squibb
Status	Ongoing

Source of Information	Trial registry[1]
Location	EU (incl UK), USA, Canada, Australia, Japan, Israel and Russian Federation
Design	Randomised, active-controlled, parallel assignment
Participants	n=550 (planned); aged 18 years and older; glioblastoma; un-methylated MGMT; newly diagnosed
Schedule	Patients received radiation therapy combined with either nivolumab (240 mg every 2 weeks for 16 weeks and then 480 mg every 4 weeks) in the experimental arm or temozolomide (TMZ) in the active comparator.
Follow-up	Not reported
Primary Outcomes	Overall survival (OS) [Time frame: Approximately 3 years]
Secondary Outcomes	• Progression free survival (PFS) [Time frame: Approximately 24 months] • Overall survival [Time frame: Approximately 24 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as October 2019

ESTIMATED COST

Nivolumab is already marketed in the UK. The NHS indicative price for nivolumab solution for infusion is as follows:[24]

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

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 in development. DCVax-L for treating newly diagnosed glioblastoma (GID-TA10143). Expected May 2019.
- 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.[25]

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