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Depatuxizumab mafodotin for newly diagnosed EGFR-amplified glioblastoma – first line

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LAY SUMMARY

Glioblastoma (GBM) is a fast-growing type of brain tumour that develops from glial cells in the brain. GBM 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; GBM is one of the most common types of brain cancer. The exact cause of GBM is not known but research has shown that changes in genes that produce a protein called 'EGFR' often leads to poorer treatment outcomes. This is now an active area of research in the search for improved treatment options for GBM.

Depatuxizumab mafodotin is a monoclonal antibody-drug conjugate that targets EGFR and is being investigated to treat GBM. It selectively targets cancer cells by circulating throughout the body until it finds the specific antigen that is over-expressed on tumour cell surfaces, releasing the toxic molecules that destroys the cancerous tumour cells. This potentially reduces the damage to normal cells in other parts of the body. Depatuxizumab mafodotin is delivered intravenously and is proposed to be used alongside the current treatment options for certain people with GBM. If licenced, it has the potential to increase the length of survival in patients with GBM.

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TARGET GROUP

EGFR-amplified glioblastoma (newly diagnosed) – first line; in addition to concomitant radiotherapy and temozolomide (TMZ)

TECHNOLOGY

DESCRIPTION

Depatuxizumab mafodotin (ABT-414) is a monoclonal antibody-drug conjugate that targets the epidermal growth factor receptor (EGFR). EGFR is known to be over-expressed in a wide variety of human tumours, and is associated with increased metastasis, decreased survival and a poor prognosis. Depatuxizumab mafodotin is designed to be stable in the bloodstream and only release the potent monomethyl auristatin F cytotoxic agent once inside the targeted cells and thus does not lead to other, usually dermatological, toxicities typically associated with other EGFR-targeted therapies.[1]

Depatuxizumab mafodotin intravenous (IV) is intended to be used to treat newly diagnosed patients with EGFR-amplified glioblastoma in addition to the current standard therapy that consists of chemoradiation and adjuvant temozolomide (TMZ).[2]

In the currently ongoing trial in newly diagnosed adults whose tumours are EGFR-amplified (NCT02573324), depatuxizumab mafodotin IV is administered on day 1 of weeks 1, 3 and 5 along with the standard therapy of TMZ and radiation during the chemoradiation phase. Depatuxizumab mafodotin is given on days 1 and 15 of each cycle along with TMZ (says 1-5 of each cycle) per standard of care during the adjuvant phase. Total treatment duration is 12 months. The follow up period is up to four years.[2]

Depatuxizumab mafodotin does not currently have Marketing Authorisation in the European Union for any indication.

INNOVATION and/or ADVANTAGES

If licensed, depatuxizumab mafodotin will offer an additional first line treatment option for newly diagnosed glioblastoma patients who currently have limited therapy options available. Glioblastoma is a condition with a poor prognosis and low median survival time and depatuxizumab mafodotin has the potential to increase overall survival patients whose tumours are EGFR-amplified.

DEVELOPER

AbbVie Ltd

PATIENT GROUP

BACKGROUND

Glioblastoma (GBM) is a malignant glioma (WHO grade IV). GBM is the most common and most malignant of the brain tumours. 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.[3,4] Glioblastomas primarily affect adults, and they are located preferentially in the cerebral hemispheres.[3]

Glioblastomas can be classified as primary or secondary tumours. Primary GBM 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.[3]

Increasing evidence indicates that primary and secondary glioblastomas constitute distinct disease entities that evolve through different genetic pathways, affect patients at different ages, and differ in response to some of the current therapies. Of all the astrocytic neoplasms, glioblastomas contain the greatest number of genetic changes, which, in most cases, result from the accumulation of multiple mutations.[3] Aberrant epidermal growth factor receptor (EGFR) signalling is common in cancer. Increased expression of wild type and mutant EGFR is a widespread feature of diverse types of cancer. EGFR gene amplification and overexpression are a particularly striking feature of glioblastoma (GBM), observed in approximately 40% of tumours, but are rare in low-grade gliomas, suggesting a causal role for aberrant EGFR signalling in the pathogenesis of GBM.[5]

Symptoms of GBM 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.[6]

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 GBMs to recur after initial treatment.[7] Current therapies remain palliative and include surgery to remove as much of the tumour as possible, followed by chemoradiation.[8] Without therapy, patients with GBMs 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.[3]

CLINICAL NEED and BURDEN OF DISEASE

Brain tumours are relatively rare. In the UK in 2015, the proportion of brain tumours out of all cancer cases was of 3%.[9]

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).[10] GBM is the most common type of malignant brain tumour. Around 55% of all brain tumours are GBMs[11] and applying that proportion to the total number of brain cancers would equate to a total of ~5,100 cases of GBMs in England in 2016.

In England in 2015, the incidence rate of brain cancer, other central nervous system and intracranial tumours (ICD-10 codes C70 to C75) was 18 per 100,000 persons.[12] 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.[13]

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.[14] 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).[15]

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.[16]

PATIENT PATHWAY

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. DCVax-L for treating newly diagnosed glioblastoma (GID-TA10143). Expected April 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 (GID-NG10003). Expected publication date 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). March 2009.

NHS ENGLAND and POLICY 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.[17]

CURRENT TREATMENT OPTIONS

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.[18]

In England, NICE technology appraisal guidance TA121 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).[19] 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.[20]

EFFICACY and SAFETY

Trial	INTELLANCE-1, NCT02573324; depatuxizumab mafodotin in addition to temozolomide and radiation therapy *versus* placebo in addition to temozolomide and radiation therapy; phase III
Sponsor	AbbVie
Status	Ongoing
Source of Information	Trial register[2]
Location	EU (incl UK), USA, Canada, countries in Latin America, Russia and South East Asia.
Design	Randomised; placebo-controlled
Participants	n=640 (planned); aged 18 to 99 years old; clinical diagnosis of glioblastoma; confirmed Epidermal growth factor receptor amplification in tumour tissue
Schedule	Randomised to depatuxizumab mafodotin (IV) in addition to oral temozolomide and radiation; or placebo (IV) in addition to oral temozolomide and radiation
Follow-up	Active treatment period not specified, follow up for up to four years
Primary Outcomes	Overall survival (OS)
Secondary Outcomes	• Number of days to deterioration in symptom severity score (MDASI-BT) • OS for the EGFRvIII-mutated tumor subgroup • OS for the O6-methylguaninemethlytransferese (MGMT) methylated subgroup • Number of days to deterioration in neurocognitive functioning on the Hopkins Verbal Learning Test Revised • Progression Free Survival (PFS) • Number of days to deterioration in symptom interference score (MDASI-BT) • PFS for EGFRvIII-mutated tumor subgroup

Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as March 2020 Study completion date reported as February 2021

ESTIMATED COST and IMPACT

COST

The cost of depatuxizumab mafodotin is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments. Requirement for EGFR amplification assay.*

☐ None identified

OTHER ISSUES

☒ Clinical uncertainty or other research question identified: *clinical study results not yet published, study ongoing*

☐ None identified

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