Depatuxizumab mafodotin is a new drug to treat a type of brain cancer called recurrent EGFR-amplified glioblastoma multiforme. Glioblastoma is the most common type of brain cancer and develops from cells that support the nerve tissue. Depatuxizumab mafodotin may offer a new treatment option for patients with recurrent EGFR-amplified glioblastoma multiforme whose first treatment has failed and may improve survival when other drugs have failed to work.
TARGET GROUP

- Glioblastoma multiforme: recurrent, in patients whose tumours are EGFR-amplified — second and subsequent line; alone or in combination with temozolomide.

TECHNOLOGY

DESCRIPTION

Depatuxizumab mafodotin (ABT-414/806, 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.

In the phase II clinical trial, depatuxizumab mafodotin 1.0mg/kg is administered via intravenous (IV) infusion (30-40 minutes) every 2 weeks as a monotherapy or in combination with temozolomide.

Depatuxizumab mafodotin does not currently have Marketing Authorisation in the EU for any indication. It is in phase II/III clinical trials for newly diagnosed glioblastoma with EGFR amplification and phase II trials in non-small cell lung cancer.

INNOVATION and/or ADVANTAGES

If licensed, depatuxizumab mafodotin will offer an additional treatment option for patients with recurrent EGFR-amplified glioblastoma multiforme, a group with high unmet medical need who currently have few well-tolerated and effective therapies available.

DEVELOPER

AbbVie Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Depatuxizumab mafodotin is in phase II clinical trials.

PATIENT GROUP

BACKGROUND

Brain tumours are relatively rare, accounting for approximately 1.6% of all cancers in England and Wales. Gliomas are the most common type of brain tumour. They arise from glial cells that support the nerve cells of the brain and spinal cord. There are four main types described: astrocytoma, ependymoma, oligodendroglioma and mixed tumours. Gliomas are graded according to their likely rate of growth, from grade 1 (slowest growing) to grade 4 (fastest growing). Grade 3 and 4 gliomas are considered high grade gliomas and grade 4 gliomas are usually glioblastomas. High grade gliomas are more common in men than women and increase with age.
Patients with high grade gliomas suffer a range of symptoms which can have a severe detrimental impact on quality of life. General symptoms include raised intracranial pressure with headache, nausea, vomiting and seizures, occasionally accompanied by more global changes such as drowsiness, changes in personality and cognition. Other specific focal deficit symptoms relate to the location of the tumour, and can include difficulties with speech, vision, ambulation, dexterity, and mood disturbances. Following initial treatment for glioblastoma, most patients will experience tumour recurrence, following which, management is largely palliative.

**CLINICAL NEED and BURDEN OF DISEASE**

The annual incidence of malignant brain tumours is 8.5 per 100,000 population, equating to approximately 3,500 cases each year in the UK. High grade gliomas represent 50-60% of all primary brain tumours, occurring at an approximate incidence rate of 3-4 per 100,000 population per year in England and Wales of which glioblastoma multiforme comprises 40-45%. Glioblastoma multiforme is the most aggressive subtype of glioma with a median survival of 18 months, and a five year survival rate of approximately 4%. Survival following recurrence is around 9-10 weeks and response to treatment for recurrent glioblastoma multiforme is seen in less than 10% of cases. Expert opinion states that many patients are not fit for further treatment at progression and will die soon after. Expert opinion also estimates that about 90% of relapses represent local rather than distant spread, and there are around 800 patients per year who relapse after concurrent chemoradiotherapy in England.

In 2014-15, there were 15,697 hospital admissions for malignant neoplasm of brain (ICD-10 C71), resulting in 94,413 bed days and 20,223 finished consultant episodes. In 2014, 3,681 deaths were registered in England and Wales due to malignant neoplasm of the brain.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Glioblastoma – bevacizumab (ID80). Expected date of issue to be confirmed. (GID-TAG413)

a Expert personal communication.
CURRENT TREATMENT OPTIONS

Once a glioblastoma recurs, treatment options are usually limited and no uniformly accepted standard of care exists. Treatment of recurrent glioblastoma multiforme should be individualised, depending on patient’s clinical condition and performance status, age and quality of life. The standard treatment options for glioblastoma multiforme include:

- Surgical resection.
- Radiotherapy.
- Concomitant adjunctive chemotherapy.
- Nitrosourea monotherapy and combination regimens (e.g. carmustine, lomustine, nimustine, fotemustine). These are DNA alkylating agents that cross the blood–brain barrier and have been extensively used in glioma treatment.
- Temozolomide, as monotherapy or in combination regimens.

Temozolomide is recommended as an option for treating glioblastoma multiforme or anaplastic astrocytoma, in those who show recurrence or progression after standard therapy (given a Karnofsky performance status score of 70 or more and have a life expectancy of 12 weeks or more). Expert opinion states that the usual practice is to rechallenge with temozolomide if there has been an interval between finishing adjuvant temozolomide and progression. If progression has occurred on temozolomide, it is assumed they are resistant to this agent and patients are usually treated with combination chemotherapy. The overall survival of patients with glioblastoma multiforme is still poor, largely due to recurrence of tumour after initial treatment with surgical resection, radiotherapy and chemotherapy. Current treatment options for glioblastoma multiforme remains challenging and no long-term treatments are currently available.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>INTELLIGENCE 2, NCT02343406, M14-483, EORTC 1410-BTG, EudraCT2014-004438-24; depatuxizumab mafodotin alone or in combination with temozolomide (TMZ) vs lomustine or TMZ; phase II.</th>
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<td>Sponsor</td>
<td>AbbVie Ltd.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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</tbody>
</table>

b Company information.
c Expert personal communication.
### Source of information
- Trial registry

### Location
- EU (incl. UK) USA, Canada and other countries.

### Design
- Randomised, active-controlled.

### Participants
- n=240 (planned); age 18-99 yrs; confirmed primary glioblastoma multiforme with unequivocal tumour progression or recurrence; presence of EGFR amplification; World Health Organization (WHO) Performance status 0–2; ≤1 prior line of chemotherapy (concurrent and adjuvant TMZ based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy) and chemotherapy must have been completed ≤4 wks prior to randomisation; surgery completed <2 wks before randomisation and pts should have fully recovered; no prior treatment with nitrosoureas or bevacizumab; no prior radiation therapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.

### Schedule
- Randomised to depatuxizumab mafodotin 1.0mg/kg IV infusion every 2 wks as monotherapy or in combination with TMZ 150mg/m² oral daily on days 1 to 5 of the first 28-day cycle with dose escalation to 200mg/m² on days 1-5 in subsequent cycles; or lomustine 110mg/m² oral on day 1 of every 42 day treatment period for patients relapsing during TMZ treatment or within 16 wks after first day of last TMZ cycle; or TMZ 150mg/m² oral daily on days 1 to 5 for the first 28-day cycle, with dose escalation to 200mg/m² on days 1-5 in subsequent cycles for patients that relapse >16 wks after the first day of last dose of TMZ cycle.

### Follow-up
- Active treatment until treatment withdrawal criteria met (disease progression, intolerable toxicity, patients’ best interest or refusal, start of any other anti-cancer agent/modality, or pregnancy; maximum 1 year treatment for lomustine), follow up 13 months after end of accrual is required.

### Primary outcome/s
- Overall survival (OS) and progression-free survival (PFS).

### Secondary outcome/s
- PFS, overall response rate (ORR), OS in sub-group with EGFRvIII mutation.

### Expected reporting date
- Completion date reported as June 2017 (final data collection date for primary outcome measure).

### 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: expert opinion notes that 2 weekly IV infusions replace oral therapy.
- 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: expert opinion notes that patients are now surviving long enough to receive more cycles of chemotherapy.
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other
- None identified

Other Issues

- Clinical uncertainty or other research question identified
- None identified

REFERENCES

6. NIHR Horizon Scanning Centre. Cilengitide (Impetrevve) for glioblastoma multiforme. University of Birmingham, February 2012. www.hscni.nihr.ac.uk

d Expert personal communication.

