DNX-2401 is a new drug to treat a type of brain cancer called glioblastoma multiforme. Glioblastoma is the most common type of brain cancer and develops from cells that support the nerve tissue. DNX-2401 may offer a new treatment option for patients with this cancer whose first treatment has failed, and may improve survival when other drugs have failed to work.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Glioblastoma or gliosarcoma tumour: recurrent; where gross total resection is not possible or advisable – second line; in combination with pembrolizumab.

TECHNOLOGY

DESCRIPTION

DNX-2401 (adenovirus-5 delta 24 RGD; ad-delta24-RGD; Ad-DNX 2401; IE-CRAd; RGD-delta24; VLI-01A) uses a genetically modified adenovirus genome to replicate selectively in retinoblastoma-pathway (Rb) deficient cells. DNX-2401 triggers tumour cell necrosis and intratumoural immune cell infiltration. Replicated copies of DNX-2401, tumour antigens and immune factors are released on cell lysis, stimulating continued tumour response.

In an ongoing clinical trial, patients are administered a single intratumoural injection of DNX-2401 after confirmation of recurrent tumour, followed 7-9 days later with pembrolizumab 200mg via intravenous (IV) injection given every 3 weeks for 2 years or until disease progression or unacceptable toxicity¹.

DNX-2401 does not currently have Marketing Authorisation in the EU for any indication. DNX-2401 is not in late stage clinical trials for any other indication.

Pembrolizumab is currently licensed in the EU for the treatment of advanced (unresectable or metastatic) melanoma in adults and locally advanced or metastatic non-small cell lung cancer in adults whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen. Very common (≥10%) reported adverse reactions include: diarrhoea, nausea, rash, pruritus, arthralgia and fatigue².

INNOVATION and/or ADVANTAGES

If licensed, DNX-2401 will offer an additional treatment option for patients with recurrent glioblastoma or gliosarcoma, a group who currently have a very poor prognosis.

DEVELOPER

DNAtrix, Inc.

AVAILABILITY, LAUNCH OR MARKETING

DNX-2401 is a designated orphan drug in the USA for glial tumour.

DNX-2401 was awarded PRIME status for recurrent glioblastoma by the EMA in July 2016.

PATIENT GROUP

BACKGROUND

Primary brain tumours are relatively rare, accounting for approximately 1.6% of all cancers in England and Wales³. Gliomas are the most common type of brain tumour and arise from
glial cells that support the nerve cells of the brain and spinal cord. There are four main types: 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 are collectively known as glioblastomas. Grade 3 gliomas include anaplastic astrocytoma, anaplastic ependymoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma. Grade 4 gliomas are usually glioblastoma multiforme. High grade gliomas are more common in men than women and increase with age.

Glioblastoma is a primary tumour of the central nervous system composed of both malignant glial and sarcomatous elements. An estimated 1% to 8% of all malignant gliomas are gliosarcomas. Gliosarcomas have a slightly worse prognosis than glioblastomas.

Patients with high grade gliomas suffer a range of symptoms which can have a severe detrimental impact on quality of life. General symptoms arise from raised intracranial pressure, with headache, nausea and vomiting, seizures and focal neurological deficits, occasionally accompanied by more global changes such as drowsiness, changes in personality and cognition. Other specific focal deficit symptoms related to the location of the tumour 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 15 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 that there are around 800 patients per year in England who relapse after concurrent chemoradiotherapy.

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**


**NHS England Policies and Guidance**


**Other Guidance**


**CURRENT TREATMENT OPTIONS**

Once a glioblastoma recurs, treatment options are usually limited and no uniformly accepted standard of care exists11. Treatment of recurrent glioblastoma multiforme should be individualised, depending on a patient’s clinical condition and performance status, age and quality of life16. The standard treatment options for glioblastoma multiforme include10,17:

- 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 the treatment of glioma.
- 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 a life expectancy of 12 weeks or more)9. 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 chemotherapy11.

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
Current treatment options for glioblastoma multiforme remain challenging and no long-term treatments are currently available.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>CAPTIVE, NCT02798406, 2401BT-002P; DNX-2401 in combination with pembrolizumab; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>DNAtrix, Inc.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry¹.</td>
</tr>
<tr>
<td>Location</td>
<td>USA and Canada.</td>
</tr>
<tr>
<td>Design</td>
<td>Non-randomised, uncontrolled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=48 (planned); aged ≥18 yrs; single glioblastoma or gliosarcoma tumour; tumour resection not possible or not planned; tumour recurrence following resection, chemotherapy and/or radiation; Karnofsky performance status ≥70%. No multiple (≥2) separate tumours; no tumour located in brain stem or both sides of brain which would involve injecting DNS-2401 into the ventricles of the brain; no previous treatment with anti-PD1 or PD-L1 agents, gene transfer or cytolytic virus of any type.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Patients administered DNX-2401 as a single 1.0mL intratumoural injection following confirmation of recurrent tumour, followed 7-9 days later with pembrolizumab 200mg IV, given every 3 wks.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for up to 2 yrs, follow-up for up to 3.5 yrs.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Objective response rate.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Overall survival; time to tumour response; duration of response. No quality of life measurement included in trial outcomes.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as Jun 2020.</td>
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</tbody>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of DNX-2401 is not yet known. A 15mL vial of pembrolizumab (50mg) costs £1,315.00¹⁸.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services: requires intratumoural injection.
- Decreased use of existing services
- Need for new services
- 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
- None identified

Other Issues

- Clinical uncertainty or other research question identified
- None identified

REFERENCES