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Toca 511 and Toca FC for recurrent high grade glioma

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LAY SUMMARY

Gliomas are the most common type of brain tumours and they develop from cells that support the nerve cells of the brain and spinal cord. High grade gliomas refer to the fastest growing types of malignant (cancerous) gliomas that can spread into the healthy tissue. High-grade gliomas are more common in men than women, and the occurrence increases with age. Symptoms may be general or specific to the area of brain where the tumour is located. General symptoms include headache, anorexia, nausea, vomiting, seizures, drowsiness, personality changes, while more specific symptoms may include difficulties with hearing, speech, sight, movement and mood. After initial treatment, the majority of high grade gliomas will recur with worsening symptoms and quality of life.

Toca 511 administered by injection, and Toca FC administered orally, are under development for the treatment of high grade gliomas that recur after initial treatment with surgery and/or other chemotherapy. Toca 511 is a type of virus that infects the cancer cells allowing Toca FC, a type of chemotherapy, to specifically target and kill the cancer cells. The selective destruction of the cancer cells further increases the body's natural immunity which may prevent the cancer from recurring. Ongoing studies have shown that both Toca 511 and Toca FC can be well tolerated and could be added to established cancer treatments.

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TARGET GROUP

Brain tumour - recurrent high-grade glioma

TECHNOLOGY

DESCRIPTION

Toca 511 (vocimagene amiretrorepvec) is an investigational injectable retroviral replicating vector (RRV) that encodes a prodrug activator enzyme, cytosine deaminase (CD). CD is derived from yeast, and humans do not naturally have this gene. Toca 511 is a modified RRV based on Moloney γ-retrovirus with an amphotropic envelope. It preferentially infects cancer cells without direct cell lysis and encodes CD that converts the antifungal drug 5-fluorocytosine to the anticancer drug, 5-fluorouracil.[1, 2]

Toca FC is an investigational, orally administered, extended-release formulation of 5-fluorocytosine (5-FC). 5-FC is a prodrug that is inactive as an anti-cancer drug. In humans, the orally administered Toca FC is absorbed and carried through the bloodstream, crosses the blood-brain barrier and diffuses into the cancer cells. In animal models, it has been shown that 5-FC is converted into the active anticancer drug, 5-FU, at high concentrations in Toca 511-infected cancer cells that are producing CD protein. 5-FU is a well-established anti-cancer agent used in many conventional chemotherapy settings.[1, 3]

Preclinical data has shown that Toca 511 plus Toca FC may have therapeutic benefit in multiple solid tumour cancers such as metastatic colorectal, pancreatic, breast, lung, melanoma and renal cancers, all of which can all spread to the brain and other organs. Both Toca 511 & Toca FC have been well tolerated in clinical trials, hence, could be added to established cancer treatments without additional toxicity.[2, 4]

In the ongoing phase II/III clinical trial for recurrent glioblastoma or anaplastic astrocytoma (The Toca 5 trial - NCT02414165), patients randomised to the experimental arm will receive 4 mL of Toca 511 administered by injection into the wall of the subject's tumour resection cavity on day 1 (approximately 40 injections of 0.1 mL), and Toca FC, administered at 220 mg/kg/day orally for 7-day courses beginning at least 5 weeks after resection and repeated approximately every 6 weeks.[5]

Toca 511 and Toca FC does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Toca 511 plus Toca FC has a dual mechanism of action within the tumour microenvironment: in addition to the direct killing of Toca 511-infected cancer cells, 5-FU can kill neighbouring uninfected cancer cells and immune-suppressive myeloid cells, including myeloid-derived suppressor cells, as well as tumour associated macrophages. Cancer cell death results in antigen presentation and activation of T cells which stimulate the antigen-presenting cells in the tumour micro-environment to present the cancer associated-antigens to the CD4 (helper) and CD8 (killer) T cells of the immune system. This results in further induction and harnessing of these cells against the cancer associated antigens to kill more cancer cells and provide durable control of the cancer, a process called acquired immunity. This

approach is designed to selectively destroy cancer cells within the body, while leaving healthy cells unharmed.[1, 6]

DEVELOPER

Tocagen Inc.

AVAILABILITY, LAUNCH or MARKETING

Toca 511 plus Toca FC was awarded a PRIME designation by the European Medicines Agency (EMA) in July 2017 and designated as a breakthrough therapy by the US Food and Drug Administration (FDA) in February 2017, both for high grade glioma.[7]

Toca 511 plus Toca FC is a designated orphan drug in the USA for recurrent glioblastoma multiforme (January 2011) and high grade glioma (September 2017).[7]

Toca 511 plus Toca FC received a fast track designation for anaplastic astrocytoma; high-grade glioma; recurrent glioblastoma multiforme in July 2015.[7]

PATIENT GROUP

BACKGROUND

Gliomas are primary brain tumours starting in the glial cells. There are 3 main types of glioma depending on the types of brain cells affected: astrocytoma (from astrocytes), oligodendroglioma (from oligodendrocytes) and ependymoma (from ependymal cells). Gliomas sometimes can sometimes have a mix of more than one of these types or could be unspecified. Astrocytomas are the most common type of glioma in both adults and children. Astrocytomas can be low grade (slow growing) or high grade (fast growing).[8]

High grade gliomas are malignant (cancerous) tumours that develop from astrocytes. They are classified according to the grade of aggressiveness (how quickly they grow) as either grade III - anaplastic astrocytomas (AA) or grade IV - glioblastoma multiforme (GBM). These tumours often spread into the healthy tissue that surrounds the tumour. This makes them difficult to remove surgically. They most commonly arise in the cerebral hemispheres (frontal, parietal and temporal lobes) or centre of the brain (thalamus). The tumour can spread to other parts of the brain and spinal cord.[9]

In most types of gliomas, there is limited evidence of causal links which are associated with increased risk of the disease. Ionizing radiation and genetic predispositions are the most established GBM risk factors. In less than 5% of all GBM cases, there is a possibility of familial aggregation, but the underlying cause remains unknown most of the time. Most GBM cases, however, are sporadic without any genetic predisposition. Multiple susceptibility loci have also been identified as contributing to the risk of developing GBM. In addition, the exposure to electromagnetic fields, head injury, and the use of cellular phones have also been suggested as risk factors, although this remains controversial.[10]

High grade gliomas cause symptoms by invading (growing) into and/or creating pressure in nearby normal brain tissue. The most common symptoms include headaches, cognitive symptoms like memory loss, personality change, confusion, speech problems, and seizures which occur in more than

one-half of patients with grade III gliomas and about one-fourth of patients with grade IV gliomas. Other common symptoms of brain tumours include muscle weakness, visual symptoms, and changes in sensation.[11] These symptoms can have a profound effect on the quality of life of the patient as well as their ability to work and to care for themselves. A significant physical and emotional burden is often placed on carers, particularly as the disease progresses.

CLINICAL NEED and BURDEN OF DISEASE

There are over 130 different types of tumour which can occur in the brain, other parts of the CNS or intracranial region and are the ninth most common cancer in the UK (2014). There were around 11,000 new cases of brain, other CNS and intracranial tumours in the UK in 2014, that's 30 cases diagnosed every day. Malignant (high grade) glioma is the most common form of primary brain tumour accounting for 34% of all cases in England in the 2006 – 2010 period.[12] High-grade gliomas (AA and GBM) are more common in men than women, and the incidence increases with age. People diagnosed with GBM are on average older than people diagnosed with grade 3 gliomas. Brain cancer is more common in White people than in Asian or Black people.[12, 13]

Mortality data shows that brain, other CNS and intracranial tumours are the eighth most common cause of cancer death in the UK (2014), accounting for 3% of all cancer deaths. Mortality is strongly related to age, with the highest mortality rates being in older males and females although there is no evidence for an association between mortality and deprivation for either males or females in England. Malignant brain tumour mortality rates have increased overall for people aged 60-69 years and across the UK since the early 1970s, but decreased for the younger age groups. The largest increase in mortality has been in people aged 80+, with rates increasing more than 18-fold between 1971-1973 and 2012-2014.[12]

Brain tumour survival depends on many different factors, but approximately 30% of adults with high-grade gliomas survive for at least 1 year, and 15% survive for 5 years. More than 20 out of 100 people (20%) with AA and 5 out of 100 people (around 5%) with GBM survive their disease for 5 years or more after they are diagnosed. Age, performance status and tumour histology are indicators of pre-treatment prognosis. Patients with high-grade gliomas have a better prognosis if they are younger, have a better performance status, or have a grade 3 tumour.[13, 14]

In the latest Hospital Episodes Statistics (2016-2017) for England, there were 16,202 hospital admissions due to a primary diagnosis of malignant neoplasm of brain (ICD-10 code C71). This accounted for 21,516 finished consultant episodes (FCE) and 99,423 FCE bed days.[15]

The population likely to be eligible to receive Toca 511 and Toca FC for recurrent high grade glioma could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (TA23). Updated March 2016.
- NICE technology appraisal. Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (TA121). June 2007.
- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015.

- NICE cancer service guideline. Improving outcomes for people with brain and other central nervous system tumours (CSG10) June 2006.
- NICE cancer service guideline. Improving supportive and palliative care for adults with cancer (CSG4) March 2004.
- NICE interventional procedure. 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, Brada M, van den Bent MJ, et al. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2014.[16]

CURRENT TREATMENT OPTIONS

Clinical practice guidelines recommend that patients diagnosed with high grade glioma should be evaluated and the treatment plan determined by a specialised multidisciplinary team including neurosurgeons, medical and radiation oncologists, but also an expert neuropathologist and neuroradiologist. Special consideration should be given to performance status and neurological function.[16]

In the UK, treatment of high grade glioma usually consists of surgical resection where possible, followed by radiotherapy. Surgery may achieve either complete resection or partial resection of the tumour. Radiotherapy has been demonstrated to prolong survival and is usually recommended after surgery. Adjuvant chemotherapy is not considered part of standard therapy in the UK, but is used more routinely in the USA. The most frequently used regimens are a combination of procarbazine, lomustine and vincristine (PCV therapy), or single agent treatment with carmustine or lomustine.[13]

NICE guidelines indicates that temozolomide, within its licensed indications, is recommended as an option for the treatment of newly diagnosed GBM in patients with a World Health Organization (WHO) performance status of 0 or 1. Carmustine implants, within their licensed indications, are recommended 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.[13]

Temozolomide is recommended as an option for treating malignant glioma, such as GBM or AA, showing recurrence or progression after standard therapy only if the person has a Karnofsky performance status score greater than or equal to 70 and a life expectancy of 12 weeks or more.[17]

EFFICACY and SAFETY

Trial	The Toca 5 Trial, NCT02414165; Toca 511 & Toca FC Versus Standard of Care (choice of single agent chemotherapy (lomustine or temozolomide) or bevacizumab administered to subjects undergoing resection for first or second recurrence); Phase II/III
Sponsor	Tocagen Inc.
Status	Ongoing, recruiting
Source of Information	Trial registry[5]
Location	USA, Canada, Israel and Republic of Korea
Design	Randomised, active-controlled, open-label
Participants	N=380 (planned); aged 18-75 years; recurrent high grade glioma following first line multimodal therapy
Schedule	Participant are randomised to one of two treatment arms: Experimental: Toca 511/Toca FC: • Resection followed by administration of 4 mL Toca 511 administered by injection into the wall of the subject's tumour resection cavity on day 1 (approximately 40 injections of 0.1 mL) • Toca FC is an extended-release formulation of flucytosine administered at 220 mg/kg/day orally for 7-day courses beginning at least 5weeks after resection and repeated approximately every 6 weeks. Active Comparator: Lomustine, Temozolomide, or Bevacizumab: Investigator selects one of the following: • Bevacizumab: Beginning 6 weeks after tumour resection, bevacizumab will be administered by IV infusion at 10 mg/kg and repeated every 2 weeks. Refer to the prescribing information and to institutional guidelines for details on the administration procedure. • Lomustine: Beginning 6 weeks after tumour resection, lomustine will be administered as a single oral dose of 110 mg/m^2 and repeated every 6 weeks. Refer to the prescribing information and to institutional guidelines for details regarding the administration procedure. • Temozolomide: Beginning 6 weeks after tumour resection, temozolomide will be administered per 1 of 2 options: ○ at a dose of 50 mg/m^2 PO once daily continuously, or ○ at an initial dose of 150 mg/m^2 IV or PO once daily for 5 consecutive days per 28-day treatment cycle that may be raised to 200 mg/m^2 once daily for 5 consecutive days in the following 28-day treatment cycles
Follow-up	Not reported
Primary Outcomes	Overall survival (OS) [Time Frame: 30 December 2019]

	Time from randomization date to death due to any cause
Secondary Outcomes	• Durable Response Rate (Complete Response (CR) or Partial response (PR) ≥ 24 weeks) [Time Frame: 30 December 2019] The proportion of patients whose best response is either CR or PR lasting at least 24 weeks, according to modified Response Assessment in Neuro-Oncology (RANO) criteria • Durable Clinical Benefit Rate (CR or PR ≥ 24 weeks or SD ≥ 18 months) [Time Frame: 30 December 2019] The proportion of subjects whose best overall response is either CR or PR lasting at least 24 weeks, or stable disease (SD) lasting at least 18 months, according to modified RANO criteria • Duration of Durable Response [Time Frame: 30 December 2019] Time from documentation of durable response to disease progression or death due to disease progression • Overall Survival at 12 months [Time Frame: 30 December 2019] Time from randomization date to death due to any cause
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Dec 2019. Study completion date reported as Mar 2023.

ESTIMATED COST and IMPACT

COST

The cost of Toca 511 and Toca FC is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Increased length of survival

☐ Reduced symptoms or disability

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services: Additional staff time to administer the products

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other: *specify*

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs: Additional cost of administering the products

☐ Reduced drug treatment costs

☐ Other: *specify*

☐ None identified

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