Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING MARCH 2019

ERC1671 (Gliovac) for recurrent grade IV glioma

NIHRIO ID	10596	**NICE ID**	10152
Developer/Company	Epitopoietic Research Corporation	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase II clinical trials.

*COMMERCIAL IN CONFIDENCE

SUMMARY

ERC1671 is in development for the treatment of high grade, recurrent gliomas. Gliomas are the most common type of primary brain tumour. They develop from the glial cells that support the nerve cells of the brain and spinal cord. Glioblastoma multiforme (GBM) is the most common and most malignant of all high grade gliomas. Gliosarcoma is a rare, malignant and fast-growing type of glioma, all classified as high grade tumours. High grade gliomas are very difficult tumours to treat due to the problems in completely removing the tumour and their resistance to radiotherapy and chemotherapy.

ERC1671 is composed of whole tumour cells and cell fragments taken from the patient and three other donors with the same type of cancer. By receiving tumour cells from different people, the patient's immune system is exposed to several different tumour-associated antigens (TAA), or proteins, minimizing the chance that tumour cells might escape from the body's defences. It also is believed this approach will trigger a stronger immune response against the TAA on the patient's tumour. This strategy in combination with the immune response inherent in the patient's own cells may lead to the elimination of glioblastoma cells and offer an additional treatment option for high grade glioma patients who currently have few effective therapies available.

PROPOSED INDICATION

Glioma – recurrent grade IV glioblastoma multiforme (GBM) or gliosarcoma (GSM)[1]

TECHNOLOGY

DESCRIPTION

ERC1671 (Gliovac) is an advanced immunotherapy based on freshly extracted tumour cells and lysates that stimulates the patient's immune system to recognise and reject cancer cells. ERC1671 contains a combination of autologous tumour cells, and allogeneic tumour cells, generated from the glioma tumour tissues of three different donor cancer patients, and the lysates of all of these cells. Upon injection, this mixture stimulates the patient's immune system to mount an immune response against the tumour cells, which may lead to their destruction.[2]

ERC1671 is in phase II clinical development for the treatment of grade IV glioma when all other traditional treatments have failed.[2] In the phase II clinical trial (NCT01903330), one dose of ERC1671 (ERC-A through D) consists of whole tumour cells (between 1×10^5 and 1×10^6 cells) combined with tumour cell lysate (between 1×10^5 and 1×10^6 cells). Immediately prior to injection, 500 µg of granulocyte-macrophage colony-stimulating factor (GM-CSF) is added to each dose, and the combined volume is injected together. Cyclophosphamide is given orally (2 × 25 mg cyclophosphamide capsules per day) for 4 days (days 2–5) at the beginning of each cycle. Patients also receive 10 mg/kg bevacizumab infusion on day 1 and 15 of each 28-day cycle. The treatment will be repeated every 28 days until progression of disease or intolerance.[1,3]

The only United States Food and Drug Administration (US FDA) targeted treatment approved for recurrent GBM patients is the angiogenesis inhibitor bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). When used alone or in combination with a cytotoxic agent, it improves imaging parameters for most patients, but duration of benefits is transient and short lived. Its impact on prolonging overall survival (OS) appears limited, especially when used outside the clinical trial settings. Although bevacizumab is approved for recurrent GBM in the USA and Canada, it did not receive market authorization by the European Medicines Agency (EMA) for this indication.[3] Cyclophosphamide is not indicated in the EU/UK for glioma.[4] GM-CSF does not have Marketing Authorisation for any indication in the EU/UK.

INNOVATION AND/OR ADVANTAGES

Despite advancements in GBM care, the vast majority of patients relapse. At the time of recurrence after the first-line therapy, further treatment options are limited.[3,5,6]

The key principle underlying this particular vaccination approach is the use of a broad set of tumour antigens, derived from freshly resected whole tumour tissue – not only from the patient under treatment, but expanded to include the same from three independent GBM tissue donors. This multivalent array of autologous and allogeneic antigens is expected to reduce the chance of immune escape, which can emerge from antigenic loss or active major histocompatibility complex (MHC) downregulation and is more likely to occur when using a single- or limited-antigen targeted immunotherapy. The future promise of this treatment might also rest in the ability to combine it with bevacizumab, and potentially with immune checkpoint inhibitors – an option that will allow more powerful immune activation in the periphery as well as more aggressive local tumour immunological targeting and destruction.[3]

ERC1671 is an advanced therapy medicinal product (ATMP) within the definition of a somatic cell therapy.[7] The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

ERC1671 does not currently have Marketing Authorisation in the EU/UK for any indication.

ERC1671 is an orphan drug in the EU as of January 2014 for the treatment of glioma.[9]

PATIENT GROUP

DISEASE BACKGROUND

Gliomas are the most common type of primary brain tumour. They develop from the glial cells that support the nerve cells of the brain and spinal cord. The main types of gliomas are named according to the cells they develop from: astrocytoma, ependymoma and oligliodendroglioma. Gliomas are graded according to their likely growth rate, from grade I (slowest growing) to grade IV (fastest growing). Grade I or II tumours are considered 'low-grade' and usually classed as benign or non-cancerous. Grade III and IV tumours, known as 'high-grade', are malignant and have a worse prognosis. Glioblastoma (also known as glioblastoma multiforme or GBM), a grade IV glioma, is the most common type of astrocytoma and is the most aggressive type of brain tumour.[10]

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.[11] GSM is a primary tumour of the central nervous system composed of both malignant glial and sarcomatous components. They account for 2% to 8% of all GBM and 0.48% of all intracranial tumours.[12]

Symptoms of gliomas vary depending on the location of the brain tumour, but may include any of the following: persistent headaches, double or blurred vision, vomiting, loss of appetite, changes in mood and personality, changes in ability to think and learn, new onset of seizures, and gradual onset of speech difficulty.[13] Like most primary brain tumours, the exact cause of gliomas is not known; risk factors may include age, exposure to radiation, and a family history of glioma.[14] Maintenance of quality of life in patients with high-grade glioma is an important endpoint during treatment, and more so for GBM because of the particularly poor prognosis with short life expectancy at this stage of the disease.[15]

CLINICAL NEED AND BURDEN OF DISEASE

Brain tumours are relatively rare and are most common in older people. Around 25% of brain tumours in the UK each year are diagnosed in people aged 75 or older. This includes tumours in other parts of the central nervous system and tumours anywhere else inside the bones of the head.[16] In the UK in 2015, the proportion of brain tumours in relation to all cancer cases was 3%.[17]

In England in 2016 there were a total of 4,516 registrations of newly diagnosed cases of malignant neoplasm of brain (ICD-10 codes C71). Directly age-standardised rates were 10.4 per 100,000 and 7.0 per 100,000 in males and females respectively. Around 55% of malignant brain tumours (WHO grades III – IV) are GBM, with about 2,200 cases diagnosed each year in England. More men (about 1,300) than women (about 900) are diagnosed each year with GBM. [18,19]

In England in 2017/2018 there were 16,971 hospital admissions with a primary diagnosis of malignant neoplasm of brain (ICD-10 code C71) resulting in 22,419 finished consultant episodes (FCE), 93,022 FCE bed days and 7,826 day cases.[20]

Across the UK, the incidence rate of brain, other CNS and intracranial tumours 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.[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main aims of treatment for high-grade glioma and associated follow-up are to increase survival while maximising a patient's functional capability and quality of life, and to ensure ready and timely access to appropriate support care for patients, their relatives and carers. Treatment at relapse may include chemotherapy and/or implantable intra-tumoural chemotherapy (carmustine implants).[22]

NICE also recommends the following be taken into account when deciding on treatment options for people with recurrent high-grade glioma (grade III or IV):[23]

- Karnofsky performance status
- The person's preferences
- Time from last treatment
- Tumour molecular markers
- What their last treatment was

Best supportive care alone for high-grade glioma if other treatments are not likely to be of benefit, or if the person would prefer this, should also be considered.[23]

CURRENT TREATMENT OPTIONS

NICE recommends the following treatment options for recurrent grade III or IV glioma:[23]

- Consider PCV (procarbazine, CCNU (lomustine) and vincristine*)* or single agent CCNU (lomustine) as an alternative to temozolomide for people with recurrent high-grade glioma.
- Temozolomide is recommended as an option for treating malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, 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.

PLACE OF TECHNOLOGY

If licensed, ERC1671 will offer an additional treatment option for recurrent high grade glioma patients who currently have few effective therapies when all other treatment options have failed.

CLINICAL TRIAL INFORMATION

Trial	NCT01903330; (ERC1671/GM-CSF/cyclophosphamide)+bevacizumab vs. placebo+bevacizumab; phase II
Sponsor	Daniela A. Bota

Status	Published
Source of Information	Publication,[3] trial registry[1]
Location	USA
Design	Randomised, double-blind, placebo-controlled
Participants	n=84(planned); ≥ 18 years of age; recurrent/progressive glioblastoma or gliosarcoma (World Health Organisation grade IV glioma)
Schedule	Subjects are randomised into two arms: **Arm I: Experimental (Cycle 1 and all subsequent cycles):** • Day 1: bevacizumab • Days 2-5: cyclophosphamide • Day 6(±1): Dose 1: ERC A and GM-CSF • Day 9(±1): Dose 2: ERC D and GM-CSF • Day 12(±1): Dose 3: ERC B and GM-CSF • Day 15(±1): Dose 4: ERC C and GM-CSF and bevacizumab • Day 18(±1): Dose 5: ERC D and GM-CSF **Arm II: Placebo (Cycle 1 and all subsequent cycles):** • Day 1: bevacizumab • Days 2-5: oral placebo • Day 6(±1): Dose 1: injectable placebo • Day 9(±1): Dose 2: injectable placebo • Day 12(±1): Dose 3: injectable placebo • Day 15(±1): Dose 4: injectable placebo • Day 18(±1): Dose 5: injectable placebo One dose of ERC1671 (i.e., ERC-A through D) consists of whole tumour cells (between 1×10^5 and 1×10^6 cells) combined with tumour cell lysate (between 1×10^5 and 1×10^6 cells). Immediately prior to injection, 500 µg GM-CSF is added to each dose, and the combined volume is injected together. Cyclophosphamide is given orally (2 × 25 mg cyclophosphamide capsules per day) for 4 days (days 2–5) at the beginning of each cycle. For the control patient group, all doses ERC-A through ERC-D are replaced by placebo treatment, which contains injectable freezing medium only, supplemented with sucrose and human albumin. No GM-CSF is added. Oral cyclophosphamide is replaced by oral placebo. Patients in both groups, active treatment group as well as placebo group, receive 10 mg/kg bevacizumab infusion on day 1 and 15 of each 28-day cycle. The timeline for days 1 through 5 (bevacizumab, followed by cyclophosphamide) is implemented strictly, whereas subsequent administration of each individual dose (in combination with GM-CSF) is flexible by ±1 day. ERC-D is the autologous component, whereas ERC-A, -B and -C are allogeneic components from three different GBM patient donors. Both groups, active treatment group and placebo group, receive bevacizumab on day 1 and 15 (±1) of each cycle.
Follow-up	The treatment will be repeated every 28 days until progression of disease or intolerance.
Primary Outcomes	**Safety [Time frame: 6 months]**

	• Safety will be assessed by clinical laboratory tests, physical examinations, vital sign measurements and the incidence and severity of adverse events (AEs) (graded according to Common Toxicity Criteria for Adverse Effects (CTCAE) v 4.0.).
Secondary Outcomes	**Efficacy [Time frame: 6 months]** • Patients will be followed both clinically and radiographically every 6 weeks for evidence of tumour progression. Tumour response will be assessed using the Macdonald criteria. Progression-free survival will be defined as the time from day 1 to the date of progression or death due to any cause. Overall survival (OS) time will be measured from day 1 until death. **Immune Response [Time frame: 6 months]** • The patient's immune response evaluation will include cytotoxic T lymphocytes (CTL) (CD3+/cluster of differentiation (CD)8+) and Treg (CD3+/CD4+/cluster of differentiation 25+ (CD25+)/CD127low) populations where CD refers to cluster of differentiation. Cytokine analyses should initially be limited to IFN-ɣ, TNF and IL-6. Further immune studies should include transforming growth factor (TGF)-B2, IL-12, IL-10.
Key Results	**Interim results:** • Median OS of patients treated with ERC1671 plus bevacizumab was 12 months. In the placebo plus bevacizumab group, median OS was 7.5 months. The maximal $CD4^+$ T-lymphocyte count correlated with OS in the ERC1671 but not in the placebo group.
Adverse effects (AEs)	• Clinical results for toxicity show an equal distribution of AEs between the active treatment and placebo groups, with no grade 4 or 5 toxicities. Among documented grade 3 toxicities, headaches were the most common. Among all toxicities, injection site reactions (induration, erythema and ulceration) were most frequently noted. Although these skin reactions were mild, they indicated the development of immune responses. However, they were not consistently noted in all patients, and hence no clear correlation between efficacy and erythema response can be concluded. Similarly, other observed mild systemic reactions, including self-limiting fever and chills, represent expected outcomes related to the intended immune stimulation.
Expected reporting date	Estimated primary completion and study completion of March 2023.

ESTIMATED COST

The cost of ERC1671 is not yet known.

ADDITIONAL INFORMATION

Epitopoietic Research Corporation did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Asunercept for treating glioblastoma (GID-TA10227). Expected publication date to be confirmed.
- NICE technology appraisal. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (TA23). April 2001. Last updated March 2016.
- NICE technology appraisal. Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (TA121). June 2007.
- NICE guideline. Brain tumours (primary) and brain metastases in adults (NG99). July 2018.
- NICE interventional procedure guidance. Photodynamic therapy for brain tumours (IPG290). 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: 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. 2014.[24]
- NICE cancer service guideline. Improving outcomes for people with brain and other central nervous system tumours (CSG10). June 2006.[22]

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