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Asinercept (Apocept) for glioblastoma multiforme for first or second line

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LAY SUMMARY

Glioblastoma multiforme (GBM) is the most common type of brain cancer and, although the cancer cells do not spread to other parts of the body, it remains the most difficult to treat. GBM is more common is older men than in women. People with this condition can suffer from a range of symptoms and impairments that affect their quality of life and that of their careers. Currently there is no cure, and people diagnosed with GBM have a life expectancy of approximately six months. Standard treatment includes removal of the tumour but in most of the cases the cancer is not eliminated and the tumour grows back.

Asinercept is an anticancer drug that is administered intravenously and acts by helping the cancer cells to induce their own death by avoiding the proliferation and migration of cancer cells in the brain. If approved, asinercept would provide an alternative treatment to patients that currently do not have other options once the standard of treatment has failed.

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TARGET GROUP

Glioblastoma multiforme – first line or second line in combination with radiotherapy (standard treatment).

TECHNOLOGY

DESCRIPTION

Asinercept is administered as an intravenous infusion. It is a soluble antibody-like recombinant fusion protein combining the extracellular domain of the CD95 receptor (CD95) and the Fc portion of IgG. [1]

CD95 (Fas, APO-1) is a pleiotrophic receptor that regulates tissue homeostasis. During cancer progression, CD95 is frequently downregulated or tumour cells are rendered apoptosis resistant. CD95 activation in glioblastoma leads to invasive growth and migration facilitated by increased expression of matrix metalloproteinases (MMP), which are key mediators of glioma invasiveness.[2] Asinercept acts by binding to the CD95-ligand (CD95L) and inhibits the activation of the CD95 pathway by CD95L. By binding to CD95L, asinercept blocks the CD95 ligand from binding to CD95, reducing cancer-cell migration in malignant glioma and protecting tumour infiltrating immune cells from apoptosis.[3]

In the phase II trial (NCT01071837), asinercept was administered at 400 mg weekly as a 30-minute (IV) infusion until progression or undue toxicity. It was started on the same day as the radiotherapy. [4]

Asinercept does not currently have Marketing Authorisation in the EU for any indication.

In the EU, asinercept was designated orphan drug in 2006 for the treatment of Graft Versus Host Disease (GVHD) and in 2010 for recurrent glioblastoma multiforme.[5]

Asinercept is currently in phase II trials for recurrent glioblastoma multiforme (GBM) for second line therapy, and is in phase I trials for Myelodysplastic syndrome and Graft Versus Host Disease.

INNOVATION and/or ADVANTAGES

Glioblastoma can be very difficult to treat due to several complicating factors such as the variety of tumour cells involved,[9] potential damage to the brain, limited capacity of the brain to auto repair and the fact that many drugs do not cross the blood-brain barrier to act on the tumour.[6] Current standard treatment includes maximal safe surgical resection, radiotherapy, and concomitant and adjuvant chemotherapy with temozolomide. At the moment, no treatment is curative.[7]

If licensed, asinercept will offer an additional treatment option for patients diagnosed with GBM for which there are limited therapeutic options available after the current standard of care has failed.

DEVELOPER

Apogenix GmbH.

AVAILABILITY, LAUNCH or MARKETING

Asinercept was awarded PRIME status for glioblastoma by the European Medicines Agency in May 2017.[8]

Anticipated EU or UK licencing dates are not available.

PATIENT GROUP

BACKGROUND

Gliomas comprise a heterogeneous group of neoplasms that differ in location within the central nervous system, in age and sex distribution, in growth potential, in extent of invasiveness, in morphological features, in tendency for progression, and in response to treatments. Glioblastoma multiforme (GBM) is by far the most common and most malignant of the glial tumours.[7]

Glioblastomas primarily affect adults, and they are located preferentially in the cerebral hemispheres. Much less commonly, GBM can affect the brainstem (especially in children) and the spinal cord. These tumours may develop from lower-grade astrocytomas (World Health Organization [WHO] grade II) or anaplastic astrocytomas (WHO grade III), but, more frequently, they manifest without any evidence of a less malignant precursor lesion. Glioblastomas are usually highly malignant—a large number of tumour cells are reproducing at any given time, and they are nourished by an ample blood supply. Dead cells may also be seen, especially toward the centre of the tumour. Because these tumours come from normal brain cells, it is easy for them to invade and live within normal brain tissue. However, glioblastoma rarely spreads elsewhere in the body.[9]

Glioblastomas can be classified as primary or secondary. Primary glioblastoma multiforme accounts for the vast majority of cases (60%) in adults older than 50 years. These tumours manifest de novo (e.g. without clinical or histopathologic evidence of a pre-existing, less-malignant precursor lesion), presenting after a short clinical history, usually less than 3 months. Secondary glioblastoma multiforme (40%) typically develop in younger patients (<45 y) through malignant progression from a low-grade astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III).[7]

CLINICAL NEED and BURDEN OF DISEASE

In England approximately 2,200 cases of GBM are diagnosed each year.[10] Is most common in men than in women (approximately 1,300 cases versus 900). Prognosis is very poor with median survival around 6 months. A study of glioblastoma in England from 2007 to 2011 estimated an overall national age standardised incidence of 4.64 per 100,000 person per year.[11] Incidence increases with age and median survival overall is of 6.1 months. Five year survival rate is of 3.4%.[11]

In Europe, glioblastoma multiforme is the most frequent primary brain tumour, accounting for approximately 12-15% of all intracranial neoplasms and 50-60% of all astrocytic tumours. In most European and North American countries, incidence is approximately 2-3 new cases per 100,000 people per year.[7]

In the latest Hospital Episodes Statistics (2015-2016) for England there were 21,219 finished consultant episodes for malignant neoplasm of brain (ICD-10 code C71), 16,408 admissions and 97,598 bed days.[12]

People with malignant glioma can suffer from a range of symptoms and impairments. Some symptoms may be general and others may be specific to the area of brain where the tumour is located. General symptoms include headache, anorexia, nausea, vomiting, seizures, drowsiness, personality changes, and cognitive slowing. More focal (specific) symptoms could include difficulties with hearing, speech, ambulation, dexterity, visual difficulties, and mood disturbances. The symptoms associated with GBM 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. [13]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab for treating recurrent glioblastoma (GID-TA10126). Expected date of issue to be confirmed.
- NICE technology appraisal in development. DCVax-L for treating newly diagnosed glioblastoma (GID-TA10143). Expected date of issue to be confirmed.
- 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 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. *Annals of Oncology*. 2014 (25); (Supplement 3):iii93-iii101 Available from doi:10.1093/annonc/mdu050

CURRENT TREATMENT OPTIONS

Treatment of malignant glioma varies from country to country. In the UK, about 30% of patients receive only supportive care with steroids, with or without anticonvulsants.[13]

Newly diagnosed glioblastoma is commonly treated with surgery, if feasible, or biopsy (the tumour is removed as far as possible, but can usually not be fully excised because of the infiltrative nature of these tumours)[13] followed by radiation plus concomitant and adjuvant temozolomide.[14] 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]

The treatment of recurrent glioblastoma continues to be a moving target as new therapeutic principles enrich the standards of care for newly diagnosed disease.[14] At recurrence, options for further treatment are limited and palliative.[13] At this stage, a minority of patients are eligible for second surgery or reirradiation, based on appropriate patient selection.[14] High dose oral procarbazine used in combination with lomustine and vincristine (PCV) regimen currently constitutes standard first line chemotherapy in the UK. Lomustine alone is sometimes used as first line therapy. The likelihood of response depends on age, tumour type and Karnofsky performance status. In general, anaplastic astrocytoma (AA) is more responsive to chemotherapy than glioblastoma multiforme (GBM). [14]

Chemotherapy is given in cycles. PCV is given for 28 consecutive days in 56‑day cycles, or for 21 consecutive days in 42‑day cycles, usually for a maximum of 6 cycles. Therapy is usually stopped after 2 cycles in those who do not respond (based on both clinical and radiological monitoring) and in those who experience significant toxicity. [14]

EFFICACY and SAFETY

Trial	NCT01071837
Sponsor	Apogenix GmbH
Status	published
Source of Information	Trial register[4]
Location	2 EU countries, not including UK, and Russia
Design	Randomised, active-controlled
Participants	N= 84; aged 18 years and older (upper age limit not specified); with a recurrence / progression of glioblastoma (first or second progression) not being eligible for tumour resection or having macroscopic residual tumour after resection of the recurrence (tumour size must 1-4 cm in T1-weighted MRI).
Schedule	Randomized in a 1:2 ratio to re-irradiation (36 Gy [2 Gy per fraction]) alone or re-irradiation (36 Gy [2 Gy per fraction]) + 400mg asinercept as a weekly intravenous infusion.
Follow-up	Patients can stay in this study as long as they benefit from the participation (no fixed end). Primary endpoint is at six months follow-up.
Primary Outcomes	Rate of progression free survival at six months (PFS-6 rate)

Secondary Outcomes	Safety and tolerability of asinercept, Progression-free survival, Objective response rates, Duration of response in responders, Overall survival, Quality of life, Cognitive function.
Key Results	PFS-6 rate in the intervention arm was of 20.7% versus 3.8% in the control (95% CI, 11.2 to 33.4) and (95% CI, 0.1 to 19.6) respectively. Median PFS was 2.5 months (95% CI, 2.3–3.8) in the control group and 4.5 months (95% CI, 3.7–5.4, P = 0.0162) in the intervention. Health-related quality of life data were available from 92% of all patients. No clinically meaningful or statistically remarkable differences between the two groups over time in any of the scales or cohorts were observed.
Adverse effects (AEs)	Any Severe AE were experienced in 37.9% of the intervention group (n=58) versus 50.0% in the control (n=13) (AEs frequency of ≥10%)
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of asinercept 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*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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