Bevacizumab (Avastin) for newly diagnosed glioblastoma multiforme – first line

SUMMARY

Bevacizumab (Avastin) in combination with temozolomide and radiotherapy is intended to be used as first line therapy for the treatment of glioblastoma multiforme (GBM). If licensed bevacizumab will represent the first targeted anti-vascular endothelial growth factor (VEGF) treatment for GBM. Bevacizumab is a humanised VEGF monoclonal antibody that inhibits VEGF induced signalling and VEGF driven angiogenesis, thereby reducing the vascularisation of tumours and subsequent tumour growth. It is currently licensed in the EU for a wide variety of solid tumours.

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 and leading to around 3,500 new cases per year in the UK. In 2011, there were 3,443 registered deaths due to primary brain tumours in England and Wales. Median survival time from initial diagnosis is 11-12 months for GBM and is principally related to age and performance status. Median survival of patients with good performance status treated with radical intent is in the region of 14 months, whilst the median survival in older patients is approximately 4-6 months.

Standard therapy for high grade glioma consists of surgical resection, radiotherapy and adjuvant chemotherapy. Concomitant and adjuvant temozolomide is recommended by NICE as a treatment option for newly diagnosed GBM. Carmustine impregnated wafers are occasionally inserted into the resection cavity for patients in whom 90% or more of the tumour has been resected. Other chemotherapy regimens include oral procarbazine in combination with lomustine and vincristine (PCV) as well as single-agent lomustine (only used in recurrent GBM). Bevacizumab is currently in a number of phase III trials in combination with temozolomide and radiotherapy comparing its effect on progression-free and overall survival against treatment with placebo.
TARGET GROUP

- Glioblastoma multiforme (GBM)a: newly diagnosed – first line; in combination with temozolomide and radiotherapy.

TECHNOLOGY

DESCRIPTION

Bevacizumab (Avastin; rhuMAb-VEGF) is a humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody that inhibits VEGF induced signalling and VEGF driven angiogenesis, thereby reducing the vascularisation of tumours and subsequent tumour growth. It also acts to normalise tumour vasculature, reducing permeability. This reduces vasogenic oedema, which can improve symptoms, reduce corticosteroid dependency, and may also reduce contrast enhancement on CT or MRI scans, leading to apparent radiological response in the absence of true tumour regressionb. Bevacizumab is administered via intravenous (IV) infusion at 10mg/kg every 2 weeks for 6 weeks, then a 4 week treatment break followed by 24 weeks at 10mg/kg once every 2 weeks, then 15mg/kg once every 3 weeks until disease progression.

Bevacizumab is licensed in the EU for cancers of the colon and rectum (metastatic, in combination with chemotherapy); breast (metastatic, in combination with chemotherapy); lung (metastatic or recurrent, in combination with chemotherapy); kidney (metastatic or advanced, in combination with interferon alfa) and ovary, fallopian tube and peritoneum (both advanced and recurrent platinum-sensitive, in combination with chemotherapy)1.

Common recognised adverse effects of bevacizumab (≥10%) include ovarian failure, anorexia, dysgeusia, headache, dysarthria, eye disorder, increased lacrimation, hypertension, dyspnoea, epistaxis, rhinitis, constipation, stomatitis, rectal haemorrhage, diarrhoea, exfoliative dermatitis, dry skin, skin discolouration, arthralgia, proteinuria, pyrexia, asthenia, pain, mucosal inflammation1.

Bevacizumab is also in phase III clinical trials for:
- Breast cancer (combination, adjuvant and neoadjuvant therapies).
- Carcinoid tumours.
- Cervical cancer (combination therapy).
- Diffuse large B-cell lymphoma.
- Gastric cancer (combination therapy).
- Head and neck cancer (combination therapy).
- Non-small cell lung cancer (combination and adjuvant therapies).
- Ovarian cancer, platinum-sensitive (combination therapy).
- Colorectal cancer (combination therapies).

and in phase II clinical trials for:
- Brain metastases (resulting from non-small cell lung cancer).
- Cervical cancer (combination and neoadjuvant therapies).
- Chronic lymphocytic leukaemia.
- Haemangiosarcoma.

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a WHO classification name ‘glioblastoma’.
b Expert personal communication.
• Liver cancer (combination therapy).
• Malignant melanoma.
• Multiple myeloma (combination therapy).
• Neuroblastoma.
• Neuroendocrine tumours (combination therapy).
• Non-Hodgkin’s lymphoma.
• Non-small cell lung cancer (combination therapy, first line in the elderly).
• Rectal cancer (combination and neoadjuvant therapies).
• Clear cell renal cell carcinoma (combination therapy).
• Sarcoma (combination therapies; first line in adolescents and children).
• Mesothelioma (combination therapy).

INNOVATION and/or ADVANTAGES

If licensed bevacizumab will represent the first targeted anti-VEGF treatment for GBM.

DEVELOPER

Roche Products Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Brain tumours are relatively rare, accounting for approximately 1.6% of cancers in England and Wales\(^2\). Gliomas are the most common type of brain tumour. 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. Grade 3 gliomas include anaplastic astrocytoma, anaplastic ependymoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma. Grade 4 gliomas are usually glioblastomas\(^3\). 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 and vomiting, seizures, and focal neurological deficits occasionally accompanied by more global changes such as drowsiness, changes in personality and cognition\(^4,5\). Other specific focal deficit symptoms related to the location of the tumour can include difficulties with, speech, vision, ambulation, dexterity and mood disturbances\(^4,5\). Following initial treatment for GBM, most patients will experience tumour recurrence following which, management is largely palliative\(^6\).

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011).
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 and leading to around 3,500 new cases per year in the UK\(^4\). In 2011-2012, there were 16,576 admissions for primary brain tumours in England, resulting in 105,163 bed days and 20,516 finished consultant episodes\(^7\). In 2011, there were 3,443 registered deaths due to primary brain tumours in England and Wales\(^8\). Median survival time from initial diagnosis is 11-12 months for GBM\(^6\) and is principally related to age and performance status. Median survival of patients with good performance status treated with radical intent is in the region of 14 months, whilst the median survival in older patients is approximately 4-6 months\(^5\).

### PATIENT PATHWAY

#### RELEVANT GUIDANCE

**NICE Guidance**

- NICE technology appraisal. Carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma. 2007\(^3\).
- NICE technology appraisal. Temozolomide for the treatment of recurrent malignant glioma (brain cancer). 2001\(^4\).
- NICE cancer service guidance. Improving outcomes for people with brain and other CNS tumours. 2006\(^2\).
- NICE interventional procedure guidance. Photodynamic therapy for brain tumours. 2009\(^9\).

#### EXISTING COMPARATORS and TREATMENTS

Standard therapy for high grade glioma consists of surgical resection, radiotherapy and adjunctive chemotherapy\(^2,3,4,5\). Concomitant and adjuvant temozolomide is recommended by NICE as a treatment option for newly diagnosed GBM\(^4\). Carmustine impregnated wafers are occasionally inserted into the resection cavity for patients in whom 90% or more of the tumour has been resected\(^3\). Other chemotherapy regimens include oral procarbazine in combination with lomustine and vincristine (PCV) as well as single-agent lomustine (only used in recurrent GBM)\(^3,5\).

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVAglio, NCT00943826, BO21990, 2008-006146-26; bevacizumab with radiotherapy and temozolomide vs placebo with radiotherapy and temozolomide; phase III.</td>
<td>Hoffman-La Roche.</td>
<td>Published in abstract.</td>
<td>Trial registry(^10) and abstract(^11).</td>
</tr>
<tr>
<td>NCT00884741, NCI-2009-01670, RTOG-0825, CDR0000640428, U10CA021661; bevacizumab with radiotherapy and temozolomide vs placebo with radiotherapy and temozolomide; phase III.</td>
<td>National Cancer Institute.</td>
<td>Published in abstract.</td>
<td>Trial registry(^12) and abstract(^13).</td>
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\(^c\) Expert personal communication.
<table>
<thead>
<tr>
<th>Location</th>
<th>EU (incl UK), USA, Canada and other countries.</th>
<th>USA.</th>
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<tbody>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=921; adults ≥ 18 years; newly diagnosed glioblastoma.</td>
<td>n=637; adults ≥ 18 years; newly diagnosed glioblastoma.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to:</td>
<td>Randomised to:</td>
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<tr>
<td></td>
<td>Arm 1</td>
<td>Arm 1</td>
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<td></td>
<td>Radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks in combination with oral temozolomide 75mg/m² daily for a maximum of 49 days and IV bevacizumab 10mg/kg every 2 weeks for 6 weeks. Following a 4 week treatment break, patients receive six 28-day cycles of IV bevacizumab 10mg/kg every 2 weeks in combination with oral temozolomide 150-200mg/m² daily in the first 5 days of each cycle. This is followed by IV bevacizumab 15mg/kg every 3 weeks until disease progression or unacceptable toxicity.</td>
<td>Radiotherapy in daily fractions of 2 Gy given 5 days per week for 3 weeks in combination with oral temozolomide 75mg/m² daily for 3 weeks. After the first 3 weeks of radiotherapy-chemotherapy concomitant treatment patients receive IV bevacizumab 10mg/kg every 2 weeks for 3 weeks in combination with radiotherapy in daily fractions of 2 Gy given 5 days per week for 3 weeks and oral temozolomide 75mg/m² daily for 3 weeks. Following a 4 week treatment break patients receive up to twelve 28-day cycles of IV bevacizumab 10mg/kg every 2 weeks in combination with oral temozolomide 200mg/m² daily in the first 5 days of each cycle.</td>
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<td></td>
<td>Arm 2</td>
<td>Arm 2</td>
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<tr>
<td></td>
<td>Radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks in combination with oral temozolomide 75mg/m² daily for a maximum of 49 days and IV placebo every 2 weeks for 6 weeks. Following a 4 week treatment break, after which patients receive six 28-day cycles of IV placebo every 2 weeks in combination with oral temozolomide 150-200mg/m² daily in the first 5 days of each cycle. This is followed by IV placebo every 3 weeks until disease progression or unacceptable toxicity.</td>
<td>Radiotherapy in daily fractions of 2 Gy given 5 days per week for 3 weeks in combination with oral temozolomide 75mg/m² daily for 3 weeks. After the first 3 weeks of radiotherapy-chemotherapy concomitant treatment patients receive IV placebo every 2 weeks for 3 weeks in combination with radiotherapy in daily fractions of 2 Gy given 5 days per week for 3 weeks and oral temozolomide 75mg/m² daily for 3 weeks. Following a 4 week treatment break patients receive up to twelve 28-day cycles of IV placebo 10mg/kg every 2 weeks in combination with oral temozolomide 200mg/m² daily in the first 5 days of each cycle.</td>
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**Follow-up**

Active treatment until disease progression.  
Active treatment until disease progression.

**Primary outcome/s**

Progression-free survival (PFS) assessed by investigator; overall survival (OS).  
OS; PFS.

**Secondary outcome/s**

PFS assessed by independent review facility; one-year survival; two-year survival; duration of stable/improved health related quality of life (HRQoL); adverse effects.  
Treatment-related toxicity; molecular profile.

**Key results**

For bevacizumab vs placebo respectively: PFS, 56% improvement reported in bevacizumab arm (p<0.0001); median OS, 16.1 mnths vs 15.7 mnths (p=0.21); PFS, 10.7 mnths vs 7.3 mnths.
PFS, 10.6 mnths vs 6.2 mnths (p<0.0001); OS, 16.8 mnths vs 16.7 mnths (p=0.214); PFS independent review committee, 64% improvement in bevacizumab arm (p<0.0001); one-year survival, 72% vs 66% (p=0.052); time to initiation of corticosteroids, 12.3 mnths vs 3.7 mnths.

(p=0.007); molecular profile, neither the 9 gene signature nor MGMT\(^d\) predicted selective benefit for bevacizumab treatment, but best prognosis patients (MGMT methylated, favourable 9-gene) had a worse survival trend with bevacizumab (15.7 months vs 25.0 months; p=0.08).

Adverse effects (AEs)

AEs consistent with known bevacizumab AEs. Increased toxicity seen in grade ≥ 3 AEs with bevacizumab, mostly neutropenia, hypertension and DVT/PE.

Expected reporting date

Estimated study completion date Oct 2013. Previously reported as July 2013.

Trial

NCT01860638, MO28347, 2012-003138-17; bevacizumab with radiotherapy and temozolomide vs placebo with radiotherapy and temozolomide; phase III.

NCT01209442, 10-0274.cc, AVF4733s; bevacizumab with radiotherapy and temozolomide; phase II.

Sponsor

Hoffman-La Roche. University of Colorado; Genentech.

Status

Ongoing. Ongoing.

Source of information

Trial registry\(^14\). Trial registry\(^15\).

Location

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

Design

Randomised, placebo-controlled. Uncontrolled, single arm.

Participants

n=510 (planned); adults ≥ 18 years; newly diagnosed glioblastoma. n=30 (planned); adults ≥ 18 years; WHO grade IV primary malignant glioma (GBM or gliosarcoma).

Schedule

All patients initially receive daily fractions of radiotherapy 2 Gy given 5 days per week, temozolomide (standard dose) and IV bevacizumab 10mg/kg every 2 weeks followed by 15mg/kg every 3 weeks until disease progression. Following disease progression, patients are randomised to IV bevacizumab 5mg/kg/week or IV placebo in combination with standard of care.

Hypofractionated intensity-modulated radiation therapy (IMRT) (60 Gy in 10 fractionations) in combination with oral temozolomide 75mg/m\(^2\) daily and IV bevacizumab 10mg/kg on day 1 and 15 (day 1 and the 1st fractionation of IMRT must start on the same day). If there is no evidence of disease progression on MRI 4-6 weeks following treatment, patients receive six 28-day cycles of IV bevacizumab at 10mg/kg on day 1 and 15 of each cycle in combination with oral temozolomide 150-200mg/m\(^2\) daily on days 1-5 of each cycle.

Follow-up

Active treatment until disease progression. Active treatment until disease progression.

Primary outcome/s

OS. PFS.

Secondary outcome/s

PFS; response rate; disease control rate; duration of response; safety; HRQoL; neurocognitive function tests; resource utilisation. OS.

\(^d\) Methylguanine-DNA methyltransferase (MGMT) gene promoter status - MGMT is an enzyme that repairs DNA damage at a site commonly targeted by cytotoxic drugs, thereby inhibiting the effect of chemotherapy on tumours. MGMT promoter methylation has been associated with extended overall survival and progression-free survival.
<table>
<thead>
<tr>
<th>Expected reporting date</th>
<th>Estimated study completion date May 2018.</th>
<th>Estimated study completion date Dec 2014.</th>
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| Trial | NCT01013285, CDR0000628787, P30CA016042, UCLA-0604016, AVF3770s, IRB#06-04-016-03B, GENENTECH-UCLA-0604016; bevacizumab with temozolomide and radiotherapy; phase II. | NCT01740258, Pro00038098; bevacizumab with temozolomide and radiotherapy; phase II. |

| Sponsor | Jonsson Comprehensive Cancer Centre; National Cancer Institute. | Duke University; Genentech. |

| Status | Ongoing. | Ongoing. |

| Source of information | Trial registry¹⁶. | Trial registry¹⁷. |

| Location | USA. | USA. |

| Design | Uncontrolled, single arm. | Uncontrolled, single arm. |

| Participants | n=70 (planned); adults ≥ 18 years; histologically confirmed intracranial GBM or gliosarcoma. | n=68 (planned); adults ≥ 18 years; WHO grade IV primary malignant glioma (glioblastoma or gliosarcoma). |

| Schedule | External-beam fractionated regional radiotherapy once daily, 5 days a week for 6 weeks, in combination with oral temozolomide daily for 6 weeks and IV bevacizumab every 2 weeks until disease progression or unacceptable toxicity. Following radiotherapy, patients receive oral temozolomide on days 1-5 of a 28-day cycle for up to 24 cycles in the absence of disease progression or unacceptable toxicity. | Part A  
Standard radiation therapy in combination with oral temozolomide 75mg/m² for 6-8 weeks and IV bevacizumab 10mg/kg every 2 weeks.  
Part B  
If stable at the end of part A, patients receive 12 cycles of oral temozolomide 200mg/m² on days 1-5 and IV bevacizumab 10mg/kg on days 1 and 15 of a 28-day cycle.  
Part C  
If no progression at the end of part B, patients receive IV bevacizumab 10mg/kg every 2 weeks or 15mg/kg every 3 weeks.  
Part D  
If patients progress in parts B or C, they receive bevacizumab-based therapy in combination with a chemotherapy and/or biologic agent, as determined by the treating physician. |

| Follow-up | Active treatment until disease progression. | Active treatment until disease progression. |

| Primary outcome/s | Safety and tolerability; OS. | OS. |

| Secondary outcome/s | Molecular profile (including MGMT promoter methylation). | Toxicity; PFS. |

| Expected reporting date | Estimated primary completion date June 2014. | Estimated study completion date June 2015. |
ESTIMATED COST and IMPACT

COST

Bevacizumab is marketed in the UK for a number of existing licensed indications; six cycles of bevacizumab at a dose of 10mg/kg costs approximately £11,088\(^e\). The cost of temozolomide administered at 75mg/m\(^2\) daily for 42 days is £3,600\(^f\).

IMPACT - SPECULATIVE

Impact on Patients and Carers

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

Impact on Services

- Increased use of existing services: current treatment for GBM does not require IV drug administration.
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified

Impact on Costs

- Increased drug treatment costs: new additional treatment option.
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other
- None identified

Other Issues

- Clinical uncertainty or other research question identified: Expert opinion suggests that bevacizumab is likely to be beneficial to patients in terms of delaying clinical deterioration and in reducing the need for steroids, but that it may have limited impact on mortality or length of survival\(^g\).
- None identified

REFERENCES


\(^e\)Based on average adult bodyweight 77.9kg.
\(^f\)Based on average surface area 1.7m\(^2\).
\(^g\)Expert personal communication.
11 Henriksson R, Bottomley A, Mason W et al. Progression-free survival (PFS) and health-related quality of life (HRQoL) in AVAglio, a phase III study of bevacizumab (Bv), temozolomide (T), and radiotherapy (RT) in newly diagnosed glioblastoma (GBM). Journal of Clinical Oncology 2013;31:(suppl; abstract 2005).