Avastin® in glioblastoma: Summary of clinical data

About 13,000 people each year are diagnosed with glioblastoma multiforme (GBM) in the Europe[1]. It is the most common and the most aggressive type of primary* malignant** brain tumour in adults[2], and almost all patients will die within five years of their diagnosis[3]. Most GBMs are advanced when diagnosed, and they can invade normal brain tissue and spread from the original tumour location, but rarely to areas beyond the brain[4].

Roche is committed to an extensive research and clinical trial programme to improve treatment options for patients suffering from this disease. The vast majority of GBM patients will see their cancer return when the initial therapy stops working, and currently, treatment options for patients with relapsed*** or progressive**** GBM are limited. Recent clinical studies have explored the potential of Avastin (bevacizumab) as an important new treatment option that may improve outcomes for patients with GBM after relapse or progression[5,6,7] and may also lead to additional positive impact on patients' daily lives[8].

Avastin is an antibody that specifically binds and blocks VEGF (vascular endothelial growth factor). VEGF is the key driver of tumour angiogenesis – an essential process of development and maintenance of blood vessels which is required for a tumour to grow and to spread to other parts of the body (metastasise). Avastin's precise mode of action helps control tumour growth and metastases with only a limited impact on side effects of chemotherapy.

Over half a million patients have been treated with Avastin so far. A comprehensive clinical programme with more than 450 clinical trials is investigating the use of Avastin in various tumour types (including colorectal, breast, lung, brain, gastric, ovarian, prostate and others) and different settings (advanced or early stage disease). Outlined below is key information from clinical trials of Avastin in GBM.

BRAIN

The BRAIN study was a phase II clinical trial in 167 patients with previously treated glioblastoma that evaluated Avastin, as a single agent or in combination with irinotecan† chemotherapy.

When Avastin was evaluated as a single agent, the study showed that at six months, almost half (43%) of the patients were alive without their disease getting worse, as defined by six month progression free survival (PFS-6)‡. When Avastin was combined with irinotecan, this figure was approximately 50%. In the study, nearly a third (28%) of patients responded to Avastin as a single agent, meaning tumours decreased in size by at least 50%. When Avastin was combined with irinotecan, 38% of patients responded to treatment.

In addition, patients receiving Avastin alone had a median overall survival (OS) of 9.2 months[4]; this was 8.7 months for those receiving Avastin in combination with irinotecan. Most adverse events related to Avastin in this trial appeared to be similar to those previously reported in other studies of Avastin in other solid tumours[9]. The most frequently reported adverse events in patients treated with Avastin alone were fatigue (45.2%), headache (36.9%), and hypertension (29.8%). In patients receiving Avastin and irinotecan, the most frequently reported adverse events were fatigue (75.9%), diarrhoea (74.7%), and nausea (67.1%). There were two deaths possibly associated with adverse events in the group of patients treated with Avastin alone, and one death possibly associated with adverse events in the Avastin and irinotecan group[5].

Key findings

- The response rate with Avastin alone was 28% and 38% in combination with irinotecan.
- In patients treated with Avastin as a single agent, at 6 months almost half (43%) of patients lived without their disease getting worse.
- Adverse events in the BRAIN study were consistent with those previously seen with Avastin and no new safety signals were reported.
- *The following data is under embargo until 10:45 CET Tuesday 22 September. For full information please attend the data presentation on Tuesday 22 September at 10:45 CET in Hall 7, Internationales Congress Centrum, Berlin.*
- Patients responding to Avastin-based therapy may also have a stabilisation or improvement in neurocognitive function and a reduction in their dose of steroids.

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An analysis that will be presented at ECCO ESMO 2009 showed that those patients who responded to Avastin based therapy may also have a stabilisation or improvement in neurocognitive function and a reduction in their dose of steroids, which may have a positive impact on patients daily lives[8]. Decline in neurocognitive function (the ability to think and reason, to make judgements and remember things) is a common consequence of GBM and can be distressing for both patients and their families. Steriods are an important part of managing symptoms in many patients with GBM. Avastin based treatment was associated with lower use of steroids in some patients, meaning that physicians may be able to reduce the side effects of long term steroid use (weight gain, insomnia and behavioural changes).

The BRAIN trial has recently been published in the Journal of Clinical Oncology[5].

AVAGLIO

On the basis of the results observed in the phase II BRAIN trial, a large phase III study in patients with newly diagnosed GBM is currently investigating Avastin with standard of care chemotherapy and

radiation. In this global, randomised, placebo controlled trial, patients will receive treatment with Avastin in combination with chemotherapy (temozolomide) and radiotherapy, or chemotherapy and radiotherapy alone. The co-primary endpoints of the trial are OS and PFS, and Roche plans to enrol approximately 920 patients.

Summary

Patients with GBM currently have a very poor prognosis with few prospects for cure and limited treatment options. Recent clinical trials have suggested that Avastin improves the clinical outcomes in patients with GBM[5,6,7] and may also lead to additional positive impact on patients' daily lives[8] .In addition, adverse events in the BRAIN study were consistent with those previously seen with Avastin and no new safety signals were reported[5,9]. Avastin has the potential to become a new treatment option for physicians. The potential benefits shown by Avastin in the BRAIN trial offer hope to GBM patients and their families. The study also formed the basis of the recent US and Swiss approvals of Avastin as a single agent for treating patients with GBM with progressive disease following prior therapy.

* Primary brain tumour refers to a tumour that originate in the brain.
** Malignant brain tumour refers to a tumour that is characterised by uncontrolled, invasive growth with the potential for metastasis
*** Relapsedcurrent describes cancer that has come back in a patient who was thought to be cancer free.
**** Progressive refers to cancer that is growing, spreading or worsening despite treatment.
† Irinotecan is a chemotherapy treatment derived from the bark and stem of the *Camptotheca acuminata* tree.
‡ In the BRAIN Study, PFS-6 was defined as the percentage of patients who remained alive and progression free at 24 weeks.

End

To download images and videos relating to Avastin and cancer please visit: www.thenewsmarket.com

References

1. Decision Resources, Cancer Incidence in 5 Continents Version IX, CI5 IX, World Population Prospects, Central Brain Tumor Registry of the United States, National Swedish Brain Tumour Registry
2. Central Brain Tumor Registry of the United States (CBTRUS). Primary Brain Tumours in the United States Statistical Report.
3. Stupp et al. N Engl J Med 2005; 352: 987-996.
4. Cancer Research UK. Types of primary brain tumours. Last accessed 13 August 2009 at http://www.cancerhelp.org.uk/help/default.asp?page=5014.
5. Friedman H et al. J Clin Oncol 2009; 31 August early online issue. Last accessed 1 September 2009 at http://jco.ascopubs.org/cgi/content/abstract/JCO.2008.19.8721v1.
6. Vredenburgh J et al. Clin Cancer Res 2007; 13 (4).
7. Vredenbugh J et al. J Clin Oncol 2009; 27:15s. .
8. Vredenburgh et al. ECCO 15 ESMO 34 2009; Abstract #8707. NC/SR
9. Avastin US Prescribing Information.