National Brain Tumor Society

INTRODUCTION

Today, there are only 4 drugs approved by the U.S. Food and Drug Administration (FDA) for malignant brain tumors. Avastin (Bevacizumab) is one of them. It is approved for the treatment of patients with recurrent glioblastoma multiforme (GBM), the most aggressive and deadliest form of malignant primary brain tumors. However, some doctors have been known to use it to treat newly diagnosed GBM patients, as well as patients with other brain tumors, such as astrocytomas due to the molecular similarities to GBM. Avastin has significant meaning to some of the patients and families who are facing and have fought GBM. For some, it has brought them a better quality of life during the last few months of survival. Currently, Avastin is only conditionally approved by the FDA through its accelerated approval program (learn more about the accelerated approval program here). Continued approval is based upon the results of studies aimed at demonstrating the effectiveness of the drug. As the largest nonprofit organization in the U.S. dedicated to the brain tumor community, the availability of effective therapies is a top priority for the National Brain Tumor Society. This document aims to help the brain tumor community understand the current and future issues surrounding Avastin.

OVERVIEW

In May of 2009, drug maker Genentech received accelerated approval from the FDA to use Avastin to treat brain cancer patients with recurrent GBM – meaning patients who had previously received chemotherapy and/or radiation, but had seen their tumor grow back. Avastin has been previously approved to treat a number of other cancer types.

The brain tumor patient advocacy community, including the National Brain Tumor Society, supported this decision for accelerated approval due to the lack of treatments currently available for brain tumor patients, and the fact that there was strong anecdotal evidence that Avastin was improving the quality of life in some patients.

As a condition of the accelerated approval Genentech received from the FDA to market Avastin for the treatment of GBM, it is required to conduct “post-market” studies (definition below) to demonstrate the effectiveness of the drug, based on two “endpoints,” or treatment goals, including: the extension of Overall Survival (OS) and demonstration of Progression-Free Survival (PFS), as defined below. Genentech’s post-market study is a Phase III clinical trial called AVAglio, and was designed to study newly diagnosed patients.

In the fall of 2012, Genentech issued its first results from the AVAglio study, which showed that Avastin, in combination with chemotherapy and radiation, increased PFS in newly diagnosed GBM patients by 36%. However, the preliminary OS data at the time was not statistically significant.

National Brain Tumor Society

Concurrently, a study supported by the National Cancer Institute's (NCI) Radio Therapy Oncology Group titled RTOG 0825 (led by Mark Gilbert, M.D. and Terri S. Armstrong, Ph.D., both members of the National Brain Tumor Society Medical Advisory Board) has also been studying whether Avastin in combination with temozolomide and radiation extends overall survival and progression free survival, and in addition, improves quality of life in newly diagnosed patients.

The results of both the AVAglio trial and RTOG 0825 study were released in early June.

***Definitions**

Post-market study:
As a condition of accelerated approval, a treatment's sponsor (in this case Genentech) is required by the FDA to demonstrate through a clinical trial after the drug has been on the market for a period of time (post-market) that the ultimate intended clinical benefit on a particular patient population was reached. In the case of anti-cancer medications the gold standard benefit, or endpoint, is overall survival.

Phase III trial:
A study to compare the results of people taking a new treatment with the results of people taking the standard-of-care treatment (for example, which group has better survival rates or fewer side effects). In most cases, studies move into phase III only after a treatment seems to work in phases I and II.

Progression-free survival (PFS):
Progression-free survival is the length of time during and after the treatment that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works. In brain tumors, progression-free survival is a measure of tumor progression.

Overall survival (OS):
The length of time, from either the date of diagnosis or the start of treatment, that patients with the disease live is the measure of overall survival (OS). In a clinical trial, measuring the overall survival is a primary way to see how well a new treatment works.

National Brain Tumor Society

Frequently Asked Questions (FAQ)

1. **What is Avastin?**

   Avastin is an anti-cancer drug that aims to kill a tumor by starving it of the energy source (blood) it needs to grow. Avastin is referred to as an anti-angiogenic drug. Angiogenesis is the process by which tumors are able to create their own blood vessels to feed themselves.

2. **How does Avastin work?**

   Avastin is a humanized monoclonal antibody that inhibits or blocks a protein in tumor cells called VEGF-A (vascular endothelial growth factor). Normal cells also produce VEGF, but in cancer cells VEGF is over-produced, allowing the tumor to feed its aggressive growth. By blocking VEGF, the drug is intended to prevent increased development of the blood vessels that feed the tumor, thus starving it to death.

3. **Is Avastin chemotherapy?**

   No, Avastin is not considered chemotherapy; it is a targeted anti-cancer therapy (drug). Chemotherapy is intended to kill fast-growing/multiplying cells (like cancer cells). Avastin targets a specific protein within the cancer cells that prevents the formation of new blood vessels.

4. **Who makes Avastin?**

   Avastin was developed by the San Francisco-based biotech company Genentech, which is part of the international pharmaceutical company, the Roche Group.

5. **Is GBM the only type of brain cancer Avastin treats?**
   No. Avastin is only currently approved to treat patients with recurrent GBM, and that is the main indication doctors treat with Avastin. However, some neuro-oncologists have also used Avastin “off label” (see more on off-label use below) to treat other molecularly similar brain cancers like newly diagnosed GBM patients (which is what both AVAglio and RTOG 0825 were designed to study), as well as other certain brain tumors such as astrocytomas.

6. **Where can I find out more about glioblastoma multiforme (GBM)?**

   Please see our list of GBM-specific facts and information, here.

National Brain Tumor Society

7. **Where can I find out more about the FDA's Accelerated Approval Program?**

   Please find detailed information on the FDA's Accelerated Approval Program, here, here, and here.

8. **What are the differences between the two Avastin studies (AVAglio and RTOG 0825)?**

   Both clinical trials reported data on overall survival, progression free survival and quality of life. However, there were significant differences in the methodologies of the two studies, especially in the measurement of Avastin's impact on health-related quality of life.

9. **What were the results of these two studies?**

   The AVAglio study demonstrated that Avastin, in combination with the current standard of care (temozolomide and radiotherapy), increased PFS in newly diagnosed GBM patients. However, AVAglio's data did not show statistically significant OS in GBM patients.

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   RTOG 0825's findings on PFS and OS, were roughly the same as AVAglio's (good PFS; no OS.) However, its QoL measures were actually negative, while the AVAglio trial reported positive health-related QoL results.

   More analysis needs to be done to gain clarity on how all these findings fit together, and thus where Avastin best fits into the current brain cancer treatment landscape.

10. **Why don't all GBM patients taking Avastin see an increase in OS?**

    One credible, and published, theory on why Avastin is unable to significantly improve overall survival (OS) in certain patients can be found in this report:

    GBMs, "…appear to develop adaptive responses to the therapies, leading to resistance to these treatments and the loss of a drug-included response," meaning the tumor cells are able to mutate and avoid the effects of the VEGF inhibitor.

There are many possible theories, however, and further studies would be required to understand the effects of Avastin and GBM, and why it often does not improve OS.

11. Does this mean that Avastin has little effect on GBM patients?

Not necessarily. Every person's biological make-up is different, thus different people react differently to the same therapy. As such, National Brain Tumor Society has heard anecdotal evidence from both patients and clinicians in the brain tumor community that Avastin has had a positive impact and allowed certain patients to live longer.

A reasonable follow-on question then is, "**Why would the FDA withdraw approval of Avastin if it has anecdotally improved the quality of life in some patients?**" The FDA was asked by Genentech to approve the drug for the treatment of GBM with its primary objectives being to extend overall survival and progression free survival. Genentech did not seek Avastin's approval as a palliative care treatment or a drug that is primarily intended to reduce suffering or improve quality of life. If Genentech satisfies the condition of accelerated approval, by showing in the post-market studies that it reached its stated goal, then it will likely remain approved. If it does not, then it is possible approval may be withdrawn. If the FDA withdraws approval of Avastin as a drug intended to extend overall survival, Genentech may pursue a new application for approval of Avastin as a drug that improves quality of life and will likely have to submit new data.

12. Why doesn't the positive PFS finding matter more?

To begin with, there is insufficient consensus within the medical community about the clinical relevance, and true patient impact, of PFS, as it relates to actual reduced symptoms and quality of life. There needs to be continued and robust discussions amongst researchers and clinicians about the value PFS actually provides to patients to gain more clarity for all stakeholders.

Additionally, while other international regulatory agencies may have different views of PFS, overall survival remains the "gold-standard" measurement for oncology drugs in the United States for a number of reasons. That said, the FDA recognizes that PFS is a clinical trial endpoint in oncology drugs.

13. Why is a future decision by the FDA about the approval of Avastin important to the brain tumor community? And what are the implications?

There have only been four (4) FDA approved drugs for brain tumor patients in the past 30 years. If Avastin were to ever be withdrawn as a treatment for GBM, it would reduce this number to only three (3).

That said, the FDA does not regulate the "practice of medicine," meaning they do not determine when a drug is prescribed by a doctor. If the GBM indication for Avastin is withdrawn, doctors could continue to prescribe Avastin to GBM patients "off-label" – as doctors are allowed to use an FDA approved drug even if the drug isn't approved for the specific indication they are targeting with the treatment. Therefore, as long as Avastin is still approved for other cancers, neuro-oncologists can still prescribe the drug for GBM patients if they determine it may be effective, despite the removal of the GBM indication from the labeling.

A decision by the FDA to withdraw approval for brain cancer may impact insurance coverage of Avastin, because the approved label is an important factor in the complex analysis for the reimbursement purposes (i.e. public and private insurance companies can refuse to cover the use of Avastin, even for those patients who are benefitting from the drug).

14. What is the National Brain Tumor Society's opinion on Avastin?

We want safe and effective therapies to be available so that doctors and patients can make informed decisions and have viable treatment options.

15. Why did we take this position?

National Brain Tumor Society arrived at this position after careful review of the available data, and discussions with our medical and scientific advisors, Board of Directors, and community members.

I. Avastin Issue: Additional Contacts

For more information, or if you have additional questions, please direct them to: questions@braintumor.org

AVASTIN INFORMATION SOURCES

1. **Avastin.com**
   http://www.avastin.com/patient

2. **Genentech.com**
   http://www.gene.com/about-us

3. **Reuters – Chronology of Avastin**
   http://www.reuters.com/article/2011/06/26/roche-avastin-idUSN1E75M15P20110626

4. **National Cancer Institute – Glossary**
   http://www.cancer.gov/dictionary

5. **National Cancer Institute – Angiogenesis Inhibitors**
   http://www.cancer.gov/cancertopics/factsheet/Therapy/angiogenesis-inhibitors

6. **National Cancer Institute – Q&A "Off-Label" Drugs**
   http://www.cancer.gov/clinicaltrials/learningabout/approval-process-for-cancer-drugs/page5

7. **Roche Group – Media Release**
   http://www.roche.com/media/media_releases/med-cor-2012-11-17.htm

8. **AVAglio report – UCLA Publication (Cloughesy)**
   http://neurooncology.ucla.edu/pub/04282011.pdf

9. **AVAglio clinical trial**
   http://clinicaltrials.gov/ct2/show/study/NCT00943826

10. **RTOG 0825 Study**
    http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0825

11. **OncoTargets & Therapy – Mechanism of Resistance to Bevacizumab (Cleveland Clinic)**
    http://www.dovepress.com/bevacizumab-in-high-grade-gliomas-a-review-of-its-uses-toxicity-assess-peer-reviewed-article-OTT