Cure Brain Cancer FOUNDATION

FAQs related to the listing of Avastin on the PBS in Australia

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This document aims to help the brain cancer community understand the current and future issues surrounding Avastin. We would like to thank our colleagues at National Brain Tumour Society in the USA for sharing their knowledge of this therapy and their FAQ document, which has informed the knowledge on this page.

INTRODUCTION

Avastin® (Bevacizumab) is a drug approved by the US Food and Drug Administration (FDA) for the treatment of patients with recurrent glioblastoma (GBM), the most aggressive and deadliest form of malignant primary brain tumours. However, some doctors have been known to use it to treat newly diagnosed GBM patients, as well as patients with other brain tumours, 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 life. Despite being approved by the FDA for the treatment of relapsed or refractory glioblastoma, Avastin is not available on the Pharmaceutical Benefits Scheme (PBS) in Australia for the same use. This means Australians face costs in the tens of thousands of dollars if they wish to use Avastin, which can only be granted when applied for via compassionate access from the drug manufacturer.

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 (patients who had previously received chemotherapy and/or radiation, but had seen their tumour grow back). Avastin has been previously approved to treat a number of other cancer types.

The US brain cancer community, including the National Brain Tumour Society, supported this decision for accelerated approval due to the lack of treatments currently available for brain tumour 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 was a Phase III clinical trial called AVAglio, and was designed to study newly diagnosed patients.

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

Concurrently, a study supported by the National Cancer Institute (NCI) radio Therapy Oncology Group title RTOG 0825 (led by Mark Gilbert, M.D. and Terri S. Armstrong, Ph.D., both members of the National Brain Tumour Society Medical Advisory Board) also studied whether Avastin, in combination with temozolomide and radiation, extends overall survival and progression free survival. This study also found that Avastin had little impact on OS.

***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 tumours, progression-free survival is a measure of tumours 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.

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FREQUENTLY ASKED QUESTIONS (FAQ)

1. What is Avastin?
Avastin is an anti-cancer drug that aims to kill a tumour 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 tumours are able to create their own blood vessels to feed themselves.

2. How does Avastin work?
Avastin is a humanised monoclonal antibody that inhibits or blocks a protein in tumour cells called VEGF-A (vascular endothelial growth factor). Normal cells also produce VEGF, but in cancer cells VEGF is over-produced, allowing the tumour to feed its aggressive growth. By blocking VEGF, the drug is intended to prevent increased development of the blood vessels that feed the tumour, 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” 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 tumours such as astrocytomas.

6. Where can I find out more about glioblastoma (GBM)?
Please refer to this list of GBM-specific facts and information, here.

7. What are the differences between the two Avastin studies referenced (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.

Both clinical trials reported data on overall survival, progression-free survival and quality of life (QoL). 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.

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 tumour 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, Cure Brain Cancer Foundation has heard anecdotal evidence from both patients and clinicians in the brain tumour 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 recognises 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 cancer community? And what are the implications?
There have only been four (4) FDA approved drugs for brain tumour 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.

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 labelling.

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 Cure Brain Cancer Foundation's opinion on Avastin?
We want safe and effective therapies to be available in Australia so that doctors and patients can make informed decisions and have viable treatment options. We believe Avastin falls within this category, and our full statement can be downloaded at www.curebraincancer.org.au/access.

15. Why did we take this position?
Cure Brain Cancer Foundation arrived at this position after careful review of the available data, and discussions with our independent Scientific Advisory Committee, Board of Directors, and community members.

16. What are the side effects of Avastin?
Everyone reacts differently to Avastin, and there are side effects associated with taking this therapy. It is important you know what these are. Most people do not have serious, life threatening side-effects, although some do. Your medical professional will advise you whether to continue treatment should you experience side-effects.

You can read more about the side effects on Avastin's website.

17. How much does Avastin cost overseas?
Each country is different. In the US, the drug is approved by the FDA for use on recurrent glioblastoma, meaning it is available for healthcare practitioners to prescribe their patients if they deem that course of action appropriate. Of course, the US healthcare system operates very differently to the Australian system, so the final cost (if any) will come down to which health insurer the patient is with. In Australia, patients with private health cover still have to cover the cost of this drug from their own pockets, often up to $20,000.

In the UK, the drug is not yet approved but patients in England are able to access it via the Cancer Drug Fund (CDF), a scheme designed to give patients access to drugs that are shown to be effective by are not 'cost efficient'. This is similar to compassionate access, but instead of the patient fronting the cost of the treatment, it is covered by the National Health Service on a case-by-case basis (NHS).

18. Is there anything else I should know about Avastin?
- Avastin should not be used for 28 days before or after surgery and until surgical wounds are fully healed.
- Using Avastin may make you ineligible for some clinical trials for a period of up to 30 days after treatment. You should discuss your eligibility for clinical trials with your medical professional and the impact taking Avastin may have on your ability to participate.
- You should not use Avastin if you are pregnant, planning on pregnancy, or are currently breastfeeding.